STATISTICAL REVIEW AND EVALUATION

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NDA#:	21-431
Applicant:	Lipha Pharmaceuticals
Name of Drug:	Acamprosate Tablets
Indication:	Maintenance of abstinence from alcohol in patients with alcohol dependence who have been withdrawn from alcohol and want to maintain their abstinence
Documents Reviewed:	Electronic submission dated December 21, 2001, SAS data sets and its related submissions dated January 31, 2002, March 20, 2002
Medical Officer:	Celia Winchell, M.D. (HFD-170) Efficacy Reviewer and Team Leader Michael Sevka, M.D. (HFD-170) Safety Reviewer

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This review has been discussed with the review team.

EXECUTIVE SUMMARY

Pelc II (European Trial)

A total of 188 eligible patients with 21 to 71 years of age were randomized to receive Acamprosate 1332 mg/day (n=63), Acamprosate 1998 mg/day (n=63) or placebo (n=62) for 3-months treatment of gastro-resistant Acamprosate tablets. The trial was completed in April 1992. The dropout rates appeared to be marginally different among the three treatment groups (48% in placebo, 30% in Acamprosate 1332 mg/d, 32% in Acamprosate 1998 mg/d). From either the sponsor's post-hoc defined primary efficacy endpoints (relapse rate and Cumulative Abstinence Duration (CAD)) or this reviewer's assessment of maintenance of abstinence based on no-relapse rate during the entire 3-months treatment period months and time to first relapse, the effects of low dose and median dose Acamprosate as compared to placebo were consistent and the pairwise comparisons (placebo vs. low-dose and placebo vs. median-dose) yielded statistically significant p-values. The statistically significantly higher complete abstinence rates in the Acamprosate groups were consistently observed using the last value carried forward type analysis (dropout without drinking was defined as abstinence) and the conservative analysis (dropout without drinking was defined as non-abstinence).

Paille (European Trial)

Five hundred and thirty-eight (538) eligible patients were randomized to receive Acamprosate 1332 mg/day (n=188), Acamprosate 1998 mg/day (n=173), or placebo (n=177) for 1-year (360 days) treatment. The trial was completed in November 1992. Study completion rates differed among the three treatment groups, nominal p=0.0055. It appeared that only about ½ of the patients treated with Acamprosate (52% with 1998 mg/day regimen and 45% with 1332 mg/day regimen) completed the study and a little over 1/3 of the patients treated with placebo completed the study (35%). The conservative type analyses are attractive because it might be reliably used to be sure that a patient was completely abstinent during the treatment phase. Although these methods yielded a higher complete abstinence rates with Acamprosate 1332 mg/day treatment (14% or 18%) compared to placebo (7% or 11%), the median time to first drink was essentially the same between these two groups (about 30 days) using the conservative method or the LOCF (last observation carried forward) method. In contrast, the higher complete abstinence rates with Acamprosate 1998 mg/day treatment (14% or 19%) were further supported by the time to first drink analyses using both approaches and yielded twice longer median time (about 60 days) as compared to placebo or Acamprosate 1332 mg/day treatment. The primary comparison in this study was Acamprosate 1332 mg/d and placebo. The sponsor's conclusion that "Acamprosate 1332 mg/day failed to reach significantly better results than placebo for most main efficacy criteria" was consistent with this reviewer's conclusion. It is noted that the second objective of a superior complete abstinence rate with Acamprosate 1332 mg/day was not shown through the observation phase.

PRAMA (European Trial)

A total of 272 patients received study medication were randomized to receive Acamprosate (n=136) or placebo (n=136) for 48 weeks treatment. The trial was completed in December 1992. The percentage of patients who completed the study between placebo (40%) and Acamprosate (58%) was shown to be different, nominal p=0.0004. The Acamprosate treated patients appeared to stay on study twice longer (48 weeks vs. 24 weeks) than the placebo treated patients. Acamprosate was shown to have longer time to first relapse, higher percentage of continuous abstinence and higher percentage of cumulative abstinence rate during the treatment phase as compared to placebo. Further investigation suggested that a higher percentage of patients completed the study without relapsed to drinking with Acamprosate (31%) compared to placebo (15%), and that among those who discontinued the study early, a lower percentage of Acamprosate treated patients (21%) relapsed compared to placebo treated patients (35%).

US 96.1 (US Trial)

The NDA report was dated November 19, 2001. A total of 601 patients were randomized to receive placebo (n=260), Acamprosate 2000 mg/day (n=258) (median dose), or Acamprosate 3000 mg/day (n=83) (high dose) for 24-weeks (6-months) treatment. The intent-to-treat population or the all efficacy population was based on 592 patients (256, 253 and 83, respectively). The main interest was the comparison between Acamprosate 2000 mg/day vs. placebo and Acamprosate 3000 mg/day group was a dosage exploratory arm.

The placebo arm and Acamprosate 3000 mg/day arm had one month longer exposure to the treatment than Acamprosate 2000 mg/day arm during the treatment phase and a total of two months longer exposure including the follow-up phase. In addition, the dropout rates were significantly higher with Acamprosate 2000 mg/day (59%) than with placebo (45%), nominal p=0.0015. It appeared that data indicated an informative censoring and differential dropout pattern. The median dose Acamprosate (2000 mg/day) failed to show a superior treatment effect on all the protocol specified efficacy endpoints.

The sponsor argued the need to restructure the intended statistical analysis plan because European outcome parameters that were contingent on a population abstinent at baseline (e.g., time to first drink and rate of complete abstinence) were not relevant in the largely non-abstinent US sample. In the US population, 50% of the patients had not discontinued drinking at randomization (100% in European trials) and only 10% of patients underwent medicated detoxification (primarily outpatient) (100% in European trials). Details of the differences between the three European pivotal trials (Paille, Pelc II and PRAMA) and the US 96.1 Trial can be found in the Appendix – US96.1 of this review.

The post-hoc defined primary efficacy endpoint, viz., the CCAD (corrected CAD) adjusted for the discontinuation of alcohol and the post-hoc defined covariates (baseline CGI-severity (clinical global impression-severity), stage of readiness to change, psychological antecedent, addiction index, and goal of complete abstinence) or outcome related treatment exposure, was carefully assessed. It appeared that partial inclusion of the post-hoc covariates may or may not reach a statistically significant effect with Acamprosate 2000 mg/day compared to placebo. This study did not show an effect of Acamprosate 2000 mg/day treatment without any adjustment on the covariates. Adjustment of treatment goal alone (a subjective covariate) or treatment exposure alone (a potential treatment related variable) still failed to demonstrate a significant Acamprosate 2000 mg/day effect, the primary comparison arm of interest.

From the repeated measure analysis, the GEE (generalized estimating equation) analysis and the cross sectional analysis of the total heavy drinking days and the total any drinking days, no statistically significant Acamprosate 2000 mg/day effect was observed. Acamprosate 2000 mg/day appeared to have numerically similar or more heavy drinking days than the placebo. The details were provided under the Section on US96.1 Trial.

Although Acamprosate 3000 mg/day treatment was only an exploratory arm and had only 1/3 of the patient size, it has comparable dropout rate and treatment exposure compared to the placebo. It appeared that this high dose arm might have a favorable (often statistically significant) higher percent of cumulative abstinence duration, lower number of heavy drinking days over time.

1 BACKGROUND

Acamprosate (calcium acetylaminopropanesulfonate) is a synthetic centrally acting drug with a molecular structure related to that of taurine and the neuromediator gamma-amino butyric acid (GABA). Animal and human studies of Acamprosate indicate a specific action on symptoms of alcohol dependence, which may result from antagonism of excitatory amino acids as well as some GABA-agonist action of Acamprosate. According to the submitted document, Acamprosate has been approved over the past decade in more than 30 countries worldwide, including most of Europe and Scandinavia, much of Latin America, Australia, South Africa and Hong Kong, as a therapy to maintain abstinence following alcohol withdrawal in the chronic alcohol-dependent patient.

In this priority NDA, the sponsor submitted 13 placebo-controlled clinical trials related to claims of effectiveness. Among these, the sponsor categorized them into three controlled pivotal efficacy studies (Pelc II, PRAMA and Paille), six European controlled short-term supportive studies (Poldrugo, Tempesta, UKMAS, BENELUX, ADISA, and Ladewig), one US controlled short-term supportive study (US 96.1), and three European controlled long-term supportive studies (Lesch, Barrias, Besson).

After the review team meeting of FDA, it was decided that the three European studies (Pelc II, PRAMA and Paille) and the US96.1 study were considered the pivotal efficacy studies in this review. This review pertains to the efficacy evaluation of these four trials. The medical reviewer is Dr. Celia Winchell for the efficacy evaluation and is Dr. Sevka for the safety evaluation.

It is noted that in all the 13 studies listed above, except for US96.1, Acamprosate was administered as 333 mg tablets, generally at a total daily dose of 1998 mg/day, given in 3 equal divided doses. In US 96.1, the identically formulated 500 mg tablet strength of Acamprosate was employed, at a total daily dose of 2000 mg/day, given in 2 equal divided doses (a smaller arm explored a daily dose of 3000 mg, given in 2 equal doses). According to the sponsor, "in general, drinking behavior relied on self-report of drinking between study visits, often corroborated by a second party and verified by breath, blood, or urine alcohol measurements. Drinking diaries were not used in the European studies (with the exception of UKMAS, which recorded number of abstinent days). Accordingly, in the individual study report analyses, if there was any reported drinking within an inter-visit interval, the entire interval was considered non-abstinent. In addition to a UKMAS, the other exception to this general rule was for US96.1, where patients maintained a daily drinking diary, using standard drinks, so that more precise feedback on number of drinking days and quantity of drinking was obtained."

2 PIVOTAL EFFICACY CLINICAL TRIALS

The four pivotal trials were summarized in the order of its completion.

Pelc II – a 3-month study. The trial was initiated in June 1990 and completed in April 1992.

Paille – a 360-days study. The trial was initiated in April 1989 and completed in November 1992.

PRAMA – a 48-week study. The trial was initiated in Oct. 1990 and completed in December 1992.

US 96.1 – a 24-week study. The trial was initiated in May 1997 and completed in January 1999.

Keywords: NDA review, Clinical Trials, abstinence rate, cumulative abstinence duration

Pelc II

Study of the activity and tolerance of calcium acetyl Homotaurinate (AOTA-Ca) in helping to maintain abstinence in the weaned alcoholic double-blind versus placebo

- **SYNOPSIS**

This was a multicenter (11 hospitals or clinics with 1 hospital from France and the others from Belgium), double blind, randomized placebo-controlled study. The study was initiated in June 1990 and completed in April 1992. Eligible patients weighing over 60 kgs at the start of the trial were randomized to receive Acamprosate (AOTA-Ca) 1333 mg/day (low dose), Acamprosate 1999 mg/day (median dose), or placebo. The study objective was to evaluate the effectiveness and tolerance of Acamprosate at 1333 mg/day and 1999 mg/day in helping to **maintain abstinence** in the weaned alcoholic (after the acute weaning phase) during a 3-month treatment period. There were eight visits for this three months study. Self-assessment of alcohol dependency was carried out with the aid of a booklet entitled "monitoring booklet" given to each patient. The booklet allowed for daily recording and quantification by the patient of nervousness, sleeping disorders, shaking of the hands, and desire for alcohol. The booklet was used to monitor the patient.

Note that the dosages of the Acamprosate treatment stated in the protocol were 1333 mg/day and 1999 mg/day whereas these dosages were 1332 mg/day (low dose) and 1998/2000 mg/day (median dose) in the study reports. In this review, the median dose Acamprosate group is abbreviated as 1998 mg/day group.

Statistical analysis plan stated 'quantitative parameters (variance analysis) and qualitative parameters (at minimum test of the χ^2), the progress within the group and comparison between the groups of the quantitative parameters will be analyzed according to the example of repeated measurements.' The protocol called for 'the main criterion of judgement will be the **consumption of alcohol**' and 'the other criteria will be: clinical signs linked to alcoholism = physical signs, MAST (Michigan Alcoholism Screening Test), alcohol dependency; biological signs: GT gamma, alcoholuria, transaminases; tolerance to the treatment.'

- **OVERVIEW OF THE STUDY RESULTS AND REVIEWER'S EVALUATION AND COMMENTS**

A total of 188 eligible patients with 21 to 71 years of age were randomized to receive Acamprosate 1332 mg/day (n=63), Acamprosate 1998 mg/day (n=63) or placebo (n=62). Eighty-five percent of them were males. Patients' demographics at baseline are summarized in the sponsor Table 5 (p.24 of vol.1.076). The three treatment groups appeared to be comparable at baseline.

- **PATIENT ACCOUNTABILITY**

Distribution of available patients over time is shown in Figure 1 and patients accountability is summarized in Table 1, confirmed by this reviewer. Dropout rates among the three treatment groups were 48% with placebo, 30% with low dose and 32% with median dose Acamprosate, nominal p=0.065.

The final study report amendments reclassified the discontinuation reasons in 5 placebo, 5 low dose, 2 median dose treated patients. Ten of these 12 patients were in the electronic effpt.sd2 file (patid=24 and patid=113 were not found). The completion status of these 10 patients was not changed, i.e., incompleters.

Figure 1. Distribution of available patients over time – Pelc II Trial

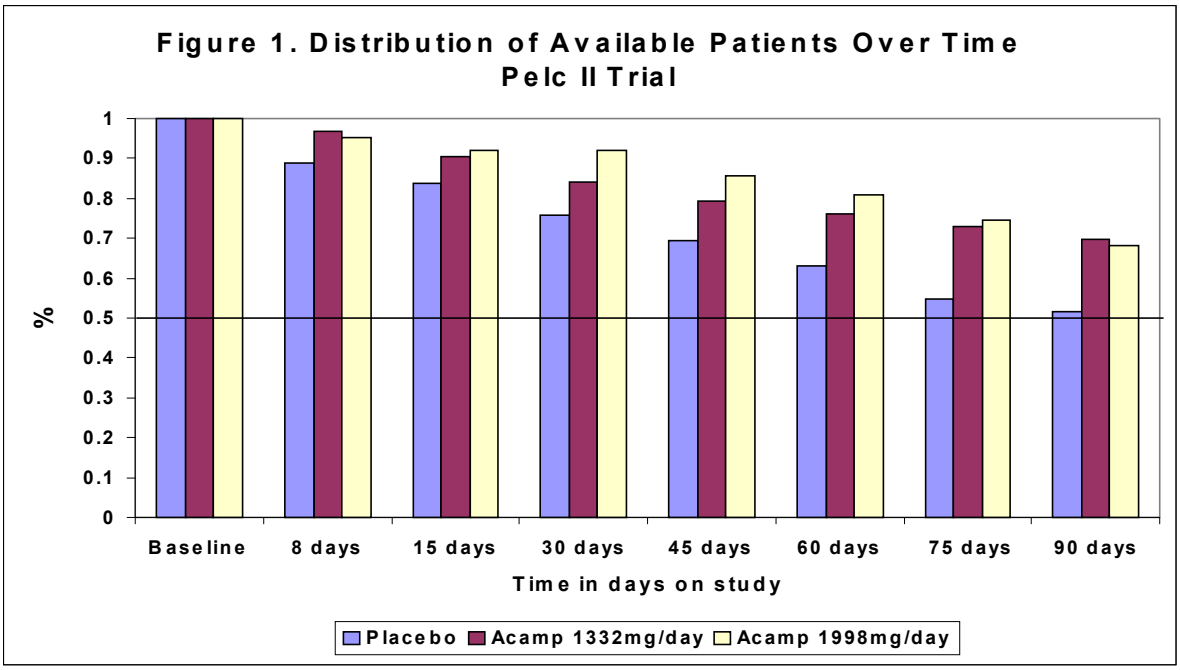


Table 1. Patients accountability – Pelc II Study (3 months trial period) [§]

Patients accountability	Treatment		
	Placebo (n=62)	Acamprosate 1332 mg/day (n=63)	Acamprosate 1998 mg/day (n=63)
Patients completing the study	32 (51.6%)	44 (69.8%)	43 (68.3%)
Patients early discontinued	30 (48.4%)	19 (30.2%)	20 (31.7%)
Severe adverse event	1 (1.6%)	2 (3.2%)	1 (1.6%)
Concurrent illness	3 (4.8%)	2 (3.2%)	1 (1.6%)
Death	0	0	0
Relapse	10 (16.1%)	6 (9.5%)	9 (14.3%)
Lost to follow-up	15 (24.2%)	6 (9.5%)	8 (12.7%)
Protocol violation	0	1 (1.6%)	0
Patient refused to continue	1 (1.6%)	1 (1.6%)	1 (1.6%)
Non-compliance	0	1 (1.6%)	0
Prohibited concomitant medication	0	0	0

[§] Extracted from the sponsor Table 2 of vol.1.076.

- **TIME TO DISCONTINUATION**

The dropout rates appeared to be different among the three groups. This reviewer further evaluated the patients' treatment exposure times, i.e., the time to discontinuation. As shown in Table 2, the estimated median time to discontinuation were quite comparable among the three treatment groups (about 85 days for all three groups), p=0.1456, non-parametric Kruskal-Wallis test.

Table 2. Distribution of time to discontinuation from the study – Pelc II[§]

	Placebo	Acamp1332 mg/day	Acamp1998 mg/day
Median (range)	84 days (4, 110)	85 days (1, 110)	85 days (6, 116)

[§] based on study duration in the electronic database

- **EFFICACY IN HELPING TO MAINTAIN ABSTINENCE**

The sponsor considered the cumulative abstinence duration (CAD) and the relapse rate as the primary efficacy variables. The sponsor also reported relapsed rate (based on the score for alcohol consumed determined at each visit). The reviewer's evaluation and comments in reference to the sponsor's summary of the study and statistical reports follow.

CAD (Cumulative Abstinence Duration)

The CAD was defined as the total number of days of abstinence and calculated as the sum of only those periods of complete abstinence. The mean cumulative abstinence duration in days were 34.4 (+/- 33.8) with placebo, 51.9 (+/- 37.2) with Acamprosate 1332 mg/d, and 56.6 (+/- 33.7) with Acamprosate 1998 mg/d groups, respectively, p=0.001, parametric 1-way ANOVA. This reviewer confirmed these results.

The distribution of CAD in each group was highly skewed. This reviewer performed a non-parametric analysis. As shown in Table 3, the median CAD was 60 days with Acamprosate low and median doses and was less than half (26.5 days) in days with placebo, overall p=0.0006. Both the low and the median dose Acamprosate treated patients had longer CAD than placebo.
To assess CAD as a fraction of the duration of treatment, the sponsor also calculated the corrected cumulative abstinence duration (CCAD). The CCAD analysis reported by the sponsor was consistent with the CAD analysis. This was probably because the treatment exposure times were very similar among the three treatment groups.

Table 3. Distribution of cumulative abstinence duration (CAD) – Pelc II Trial

	Placebo	Acamp1332	Acamp1998
Median (range)	26.5 days (0, 90)	60.0 days (0, 90)	60.0 days (0, 90)

[§] based on the variable, CAD, of the electronic submission

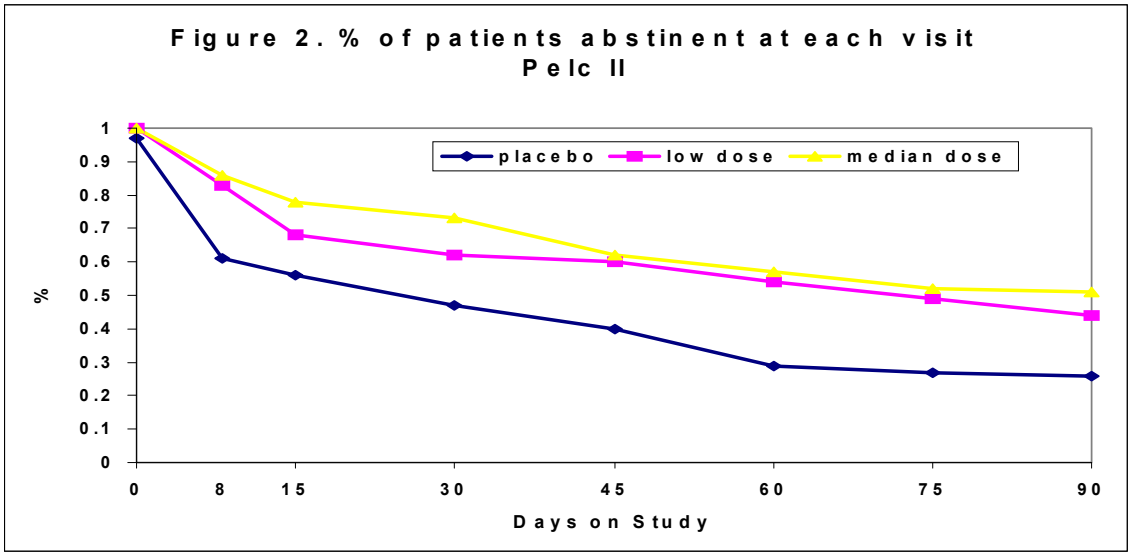
RELAPSE RATE (assessed by the score for alcohol consumed determined at each visit)

The protocol called for 'the main criterion of judgement will be the consumption of alcohol' and the summary of study from the NDA submission reported "As a primary parameter for determining efficacy, the relapse rate based on the score for alcohol consumed was determined at each visit. The alcohol consumption was rated as 0 = no alcohol; 1 = <5 drinks per day; 2 = 5-10 drinks per day; 3= >10 drinking per day. A drink was defined as 250 ml of 6^{o} beer, 120 ml of wine, 80 ml of aperitif (18^{o}) or 30 ml of 40^{o} spirit. **Only patients who consumed no alcohol were rated as abstinent and all others were considered as relapses**."

This reviewer summarized the sponsor report Table 7 (p.27 of vol.1.076) using the above criteria and classified patients as non-abstinent if the status was missing or non-abstinent, see Figure 2. The separation of the abstinence rates between the Acamprosate groups (both low and median doses) and the placebo group appeared to become apparent starting day 45 of the treatment and untill the end of the trial. At day 90, the abstinence rates were 26% with placebo, 44% with low dose Acamprosate and 51% with median dose Acamprosate, respectively. The three group comparisons yielded an overall p-value=0.013. The pairwise comparisons yielded **p-values of 0.029 (placebo vs. low dose),** 0.004 (placebo vs. median dose).

It is noted that the no-relapse rates, calculated at each visit, do not reflect the no-relapse rate over the entire treatment period.

Figure 2. % of patients abstinent at each visit – Pelc II Trial



ABSTINENCE RATE

For percentage of complete abstinence, the sponsor classified patients as abstinent if patients completed the study without relapse or patients discontinued the study early but were known clearly to have no event at day-90 (Method I). Both Acamprosate low dose and median dose treated patients appeared to have, on average, higher percentage of complete abstinence rate (43% with low dose and 41% with median dose) as compared to placebo 14.5%, p=0.0008. The pairwise comparisons yielded a nominal p-value<0.001 for both placebo vs. low-dose and placebo vs. median-dose comparisons.

Method II classified patients as abstinent only if patients who completed the study without relapse. That is, all dropouts are considered as relapsed to drinking, p=0.0011. The pairwise comparisons yielded nominal p-value < 0.001 for both low-dose vs. placebo and median-dose vs. placebo comparisons. This reviewer confirmed these analyses and the results are summarized in Table 4.

Table 4. No-relapse rates – Pelc II Trial

Method	Placebo (n=62)	Acamp1332 (n=63)	Acamp1998 (n=63)	$\chi 2$ test
I (Sponsor)	9 (14.5%)	27 (42.9%)	26 (41.3%)	0.0008§
II (Sponsor)	9 (14.5%)	26 (41.3%)	26 (41.3%)	0.0011[+]
III (Reviewer)	13 (21.0%)	32 (50.8%)	28 (44.4%)	0.0015[¦]

§ from electronic database 'RELFLAGC' – relapsed to drinking flag for ISE censored analysis
[+] from electronic database "RELFLAGU" – relapsed to drinking flag for ISE uncensored analysis, i.e., include dropouts as 'relapse', see also In-Text Table 8.7.2.7.3:1, and Table 8, p.28 of vol.1.076
[¦] this reviewer's analysis based on the patients' all visits data in the electronic database

The sponsor did not report the usual analysis based on the last observation carried forward complete abstinence status. That is, if a patient dropped out the trial early without any drinking, he/she is defined as 'abstained' while on trial. This reviewer analyzed the patients' drinking status over all the visits during the entire treatment period, i.e., a patient would be classified as no-relapse if all his/her visits had zero drinking frequency up to the time he/she discontinued the study or completed the study. This analysis is labeled as 'Method III'. The complete abstinence rates based on the Method III were 21% with placebo, 51% with Acamprosate 1332 mg/d, and 44% with Acamprosate 1998 mg/d groups, respectively. The p-value for the three-group comparison was

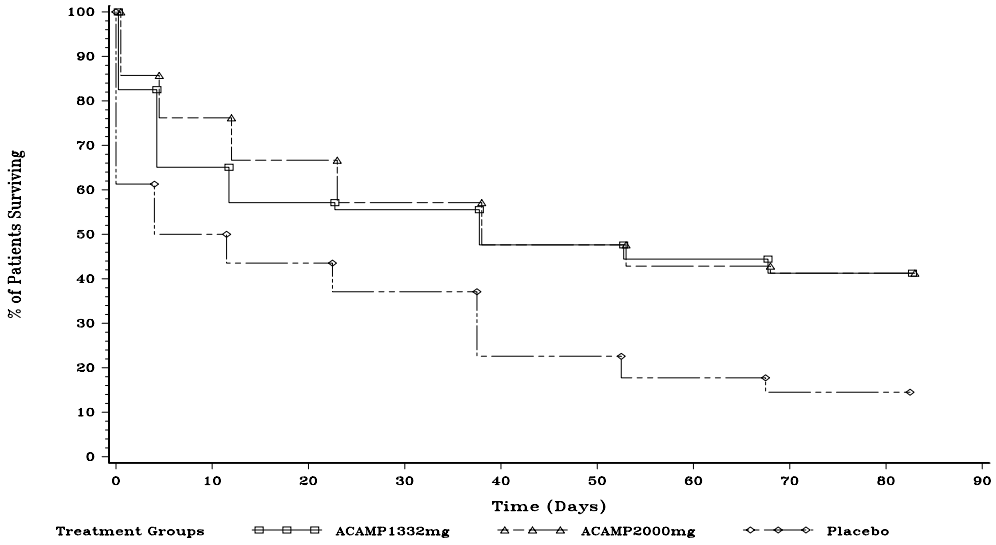
0.0015. It appeared that on average patients treated with Acamprosate low and median doses had higher percentage of complete abstinence than placebo during the three months treatment period.

TIME TO FIRST RELAPSE

In-Text Figure 8.7.2.7.2:1 Kaplan-Meier Estimate of Time to First Drink During Treatment Phase – Pivotal Efficacy Study Pelc II

The sponsor reported the analysis results of time to first relapse endpoint based on Lee-Desu Test. This reviewer used the usual log-rank test. The resulting p-values were very similar. The median time to first drink calculated from the uncensored approach was 52.5 days for the Acamprosate 1332 mg/day group, 52.5 days for the Acamprosate 1998/2000 mg/day group, and 17.0 days for the placebo group (see also In-Text Figure 8.7.2.7.2:1). It appeared that the Acamprosate 1998/2000 mg/day and Acamprosate 1332 mg/day groups had statistically significantly longer time to first relapse compared to the placebo group ($p<0.001$). The censored analysis approach (Method I) only affected one patient in the Acamprosate 1998 mg/day group, the results were very similar to the uncensored results (Method II).

Figure 8.7.2.7.2:1 Time to First relapse – Pelc II Trial



- **REVIEWER'S SUMMARY**

The dropout rates appeared to be marginally different among the three treatment groups. The median time to discontinuation was very similar (around 85 days). It is worth noting that the sponsor's report on no-relapse rate based on patients' completing the study without relapse to drinking was conservative. The no-relapse rate based on the score for alcohol consumption provided the relapse rate at each visit. But, it does not reflect the complete abstinence rate over the entire three months treatment period.

From either the sponsor's post-hoc defined primary efficacy endpoints (CAD and relapse rate) or this reviewer's assessment of maintenance of abstinence based on no-relapse rate during the entire 3-months treatment period months and time to first relapse, the effects of low dose and median dose Acamprosate as compared to placebo were consistent and the pairwise comparisons (placebo vs. low-dose and placebo vs. median-dose) yielded statistically significant p-values. The statistically significantly higher complete

abstinence rates in the Acamprosate groups were consistently observed using the LOCF type analysis (dropout without drinking was defined as abstinence) and the conservative analysis (dropout without drinking was defined as non-abstinence) imputation.

Paille (Acamprosate gastro-resistant tablets)

A multicentre controlled and double-blind comparative study of the efficacy of AOTA-Ca Studied at two dosages and placebo over a 1-year period of treatment. Followed by a 6-months post-treatment period of placebo on alcoholic patients who were followed as outpatients after withdrawal

- **PROTOCOL SYNOPSIS**

This was a multicenter (31 centers in France participated under the supervision of Professor F. Paille), double-blind, randomized, placebo controlled three arms study. The study was initiated on April 6, 1989 and completed on Nov. 19, 1992 (~3.5 years). Eligible patients with alcohol dependence of the chronic or episodic type as defined by the DSM III® classification of the American Psychiatric Association were randomized to receive placebo, Acamprosate 1332 mg/day (low dose) or Acamprosate 1998 mg/day (median dose), respectively for one year. The time schedule of the study during the one-year treatment phase followed by an additional 6 months post-treatment single blinded placebo period was as follows. The bolded visits were the main visits for the efficacy evaluation and the other visits included a rapid simplified check-up.

Visit0	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**
Assessment of Withdrawal 1wk - 1month	30days	60	**90**	120	150	**180**	240	300	**360**	420	480	**540**
	Treatment Period (1 year)									Follow-up Period (0.5yr)		

The main objectives in order of importance were as follows: (1) "to establish the therapeutic value of the administration of Aota Ca at a dosage of 1.3 g/day during 1 year in the **maintenance of abstinence** and to compare this with placebo", (2) "to evaluate the evolution of the therapeutic result during a 6-month period under placebo after discontinuation of randomized treatment and before ending the blind phase of the trial", (3) "to compare dosages by integrating the 2g/day dosage into the analysis of the French centres; furthermore, the groups treated with placebo and 2g/day Aota Ca will be included in the analysis of the European results."

The primary efficacy endpoints stated in the protocol were

A. "Clinical evaluation: after considering all the elements at his disposition, the physician will evaluate **(a) # of non-abstinent days during the month preceding the visit, (b) the average quantity of pure alcohol absorbed during these periods of non-abstinence during the preceding month."**

B. "Biological evaluation of the efficacy is based on parameters, which ensure the effect of alcohol intoxication on the patient (gamma-GT, MCV, and transaminases)."

In this study, the sponsor proposed to study 160 patients per group with a dropout rate of not exceeding 15%.

- **REVIEWER'S COMMENTS**

No statistical analysis plan was included in the original protocol. The sample size proposed was not based on the statistical principle other than setting what was thought to be a reasonable dropout rate at the time of planning. There were only four-planned visits for efficacy assessment for 1-year treatment phase and half year follow up single blinded placebo phase. They were 3-month, 6-month, 1-year and 1.5 years, as shown in table above. To evaluate the maintenance of abstinence, incidence rate of abstinence or time to first relapse may be reasonable efficacy outcomes for evaluation provided that the drinking data on abstinence over time was

reliable. According to the sponsor's response, the assessment of the first drinking was based on "the number of days between actual visits and response to the CRF question which asks the patient for the estimated number of days of non-abstinence in the last month or skips a visit, the entire visit interval since the previous visit is considered non-abstinent and the number of days of continuous abstinence since baseline is the number of days in study at the previous visit (equal zero days if the previous visit was the baseline visit)."

- **OVERVIEW OF THE SPONSOR RESULTS AND REVIEWER'S EVALUATION & COMMENTS**

- PATIENT ACCOUNTABILITY

Five hundred and thirty-eight (538) eligible patients were randomized to receive Acamprosate 1332 mg/day (n=188), Acamprosate 1998 mg/day (n=173), or placebo (n=177). The mean age at entry was 43 years old and 80% of the patients were males. Patients accountability during the treatment phase was summarized in Table 1 (submitted when seeking for approval in Europe) extracted from Table 2 of the Sponsor study report. A total of six deaths occurred, two patients from each treatment group. Details of the reason of deaths can be found in the evaluation and comments of medical review written by Dr. Cellia Winchell and Dr. Michael Sevka.

Table 1. Patient Accountability – Paille[§]

	Completed Period	Adverse Event/ Illness	Death	Improvement	Loss to Follow-up	Non Permitted medication	Other Reasons	**Refusal Non-compliance**	Relapse
Placebo n=177	62 35%	13 7%	2 1%	6 3%	28 16%	3 2%	2 1%	**25** **14%**	36 20%
A1332mg N=188	85 45%	14 7%	2 1%	5 3%	21 11%	0	2 1%	**16** **9%**	43 23%
A1998mg N=173	90 52%	10 6%	2 1%	3 2%	26 15%	0	2 1%	**12** **7%**	28 16%

[§] Extracted from Table 2 of the Sponsor study report

Study completion rates differed among the three treatment groups, nominal p=0.0055. It appeared that only about ½ of the patients treated with Acamprosate (52% with 1998 mg/day regimen and 45% with 1332 mg/day regimen) completed the study and a little over 1/3 of the patients treated with placebo completed the study (35%). The sponsor reevaluated the reasons of discontinuation after the European approval. Particularly, three placebo dropout patients had the reason re-coded as 'refusal/non-compliance'. This change made the difference in dropout rate due to refusal/non-compliance more dramatic between placebo and acamprosate.

Table 2. Patient Accountability categorized into four categories[§]

	Completed	LOE (relapse, death, refusal)	AE (AE/illness)	Others (improve, , loss to-follow-up others, non-permitted medication
Placebo N=177	62 (35%)	63 (36%)	13 (7%)	39 (22%)
A1332mg N=188	85 (45%)	61 (32%)	14 (7%)	28 (15%)
A1998mg N=173	90 (52%)	42 (24%)	10 (6%)	31 (18%)

[§] Derived from Table 1 above.

One possible way of evaluating the reasons of dropouts from the original classification may be to categorize the reasons into lack of efficacy (LOE), due to adverse events (AE), or others (Others). Table 2 above is one plausible way. With this classification, it is possible that both placebo and Acamprosate 1332 mg/day arm appeared to have higher and similar rates of lack of efficacy compared to Acamprosate 1998 mg/day arm (nominal p-value 0.061) while AE rates were similar among the three groups.

- **TREATMENT EXPOSURE**

The median exposure time was the shortest in placebo (8 months), followed by Acamprosate 1332 mg/day (10.5 months) and Acamprosate 1998 mg/day (11.8 months), see Table 3 below.

Table 3. Distribution of time to discontinuation from the study – Paille Trial

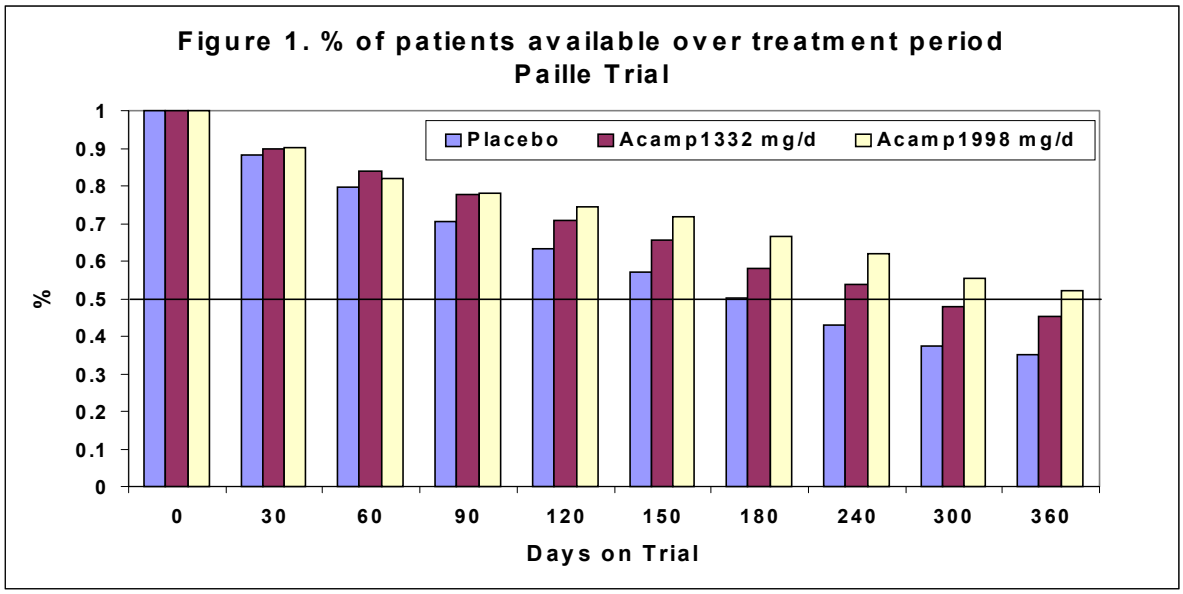
	Placebo (n=177)	Acamp1332 (n=188)	Acamp1998 (n=173)
Median (range) in days	239 days (0, 420)	320 days (0, 430)	355 days (0, 528[¦])

[§] based on study duration data

[¦] one patient has study duration longer than 430 days (i.e., 528 days). The estimated median time to discontinuation was the same when the time was set to 430 days.

Figure 1 depicted the percentages of patients completed each study visit over the treatment period. It appeared that the exposure time to the treatments varied.

Figure 1. % of patients available over treatment period – Paille Trial



- **EFFICACY ON MAINTENANCE OF ABSTINENCE**

The primary objective was "to establish the therapeutic value of the administration of Aota Ca at a dosage of 1.3 g/day during 1 year in the **maintenance of abstinence** and to compare this with placebo." Hence, the primary comparison of interest was Acamprosate 1332 mg/day vs. placebo on maintenance of abstinence over one year treatment phase.

The sponsor reported results of the following four outcomes: percentage of complete abstinence during treatment phase, time to first drink, cumulative abstinence duration (CAD) and percentage of success to address the maintenance of abstinence. The reviewer's evaluation and comments follow.

TREATMENT PHASE

PERCENTAGE OF COMPLETE ABSTINENCE

For percentage of complete abstinence, there were three analyses performed. Method I, as shown in Table 4, classified patients as abstinence if patients completed the study without relapse and discontinued the study early without relapse. Method II classified patients as abstinence only if patients completed the study without relapse. That is, all dropouts are considered as relapsed to drinking. Method III classified patients as abstinent if patients' CABST (continuous abstinence since day 0 categories) is at least 340 days (including categories 340 days and up).

The complete abstinence rate was consistently lower in placebo using all three methods. However, depending on how the abstinence status of the dropouts were imputed, the differences in abstinence rates were shown to be not statistically significant (p=0.285) using Method I, in which complete abstinence rates were 23%:27%:30% of placebo, low dose to median dose, respectively. Such differences became statistically significant (p=0.044) when the most conservative imputation was applied (Method II) with rates being 7%:14%:14%. These differences did not reach statistical significance when a benign imputation method was used, which only penalized incompleted patients to relapse if these patients had continuous abstinence less than 340 days from treatment initiation. These complete abstinence rates, using Method III, were 11%:18%:19% of placebo, low dose and median dose, p=0.096. This reviewer confirmed these analyses and the results are summarized in Table 4.

Table 4. Complete abstinence rates - Paille[§]

Method	Placebo (n=177)	Acamp1332 mg/d (n=188)	Acamp1998 mg/d (n=173)	$\chi 2$ test (global)
I	40 (22.6%)	50 (26.6%)	52 (30.1%)	.285§
II	12 (6.8%)	26 (13.8%)	25 (14.5%)	.044[+]
III	**20 (11.3%)**	**34[¦] (18.1%)**	**33 (19.1%)**	**.096[¦¦]**

[§] From electronic database "CABSTYN" - Continuous abstinence through the treatment period: y/n; or 'RELFLAGC' – relapsed to drinking flag for ISE censored analysis, i.e., included dropouts without drinking as no relapse.

[+] From electronic database "RELFLAGU" – relapsed to drinking flag for ISE uncensored analysis, i.e., included dropouts without drinking as 'relapse'.

[¦] One patient had study duration less than 360 days and was not considered as completer. When this patient was excluded from being classified as abstinence (as incompleters were coded as relapsed), p=0.107.

[¦¦] Extracted from Table 1 of the sponsor summary of study (p.5 of vol.1.083) and Table 6 of the Sponsor study reports (p.29 of vol.1.083), i.e., CABST (continuous abstinence since day 0 categories) in the category of 340 days and up.

It is noted that the primary comparison of interest pre-specified in the protocol is Acamprosate low dose vs. placebo. The p-values for this pairwise comparison were 0.377 with Method I, 0.028 with Method II, and 0.069 with Method III, respectively. This reviewer further explored the impact of the dropouts by classifying the patients into 'completer/abstinence', 'incompleter/abstinence', or 'non-abstinence' categories. It appeared that percentages of patients who were incompleter/abstinence were similar among the three groups using all three methods.

TIME TO FIRST DRINK

The sponsor reported time to first drink analysis, the Kaplan-Meier curves can be found in In-Text Figure 8.7.2.7.2:1.

This reviewer confirmed the sponsor's results and performed the analyses using three censoring methods described above. In fact, the abstinence indicators produced with the above three methods are the censoring indicators for the time to first drink analysis. Given there was a seemingly differential censoring between the Acamprosate and the placebo groups, the survival analysis yielded p=0.0695, 0.0148, and 0.0303, respectively,

for Methods I, II and III, log-Rank test. As summarized in Table 5, consistent median time to first relapse was observed using all three Methods. The median times to first drink were about two months with median dose Acamprosate and about one month for low dose Acamprosate and placebo.

In-Text Figure 8.7.2.7.2:3 Kaplan-Meier Estimate of Time to First Drink During Treatment Phase – Pivotal Efficacy Study Paille

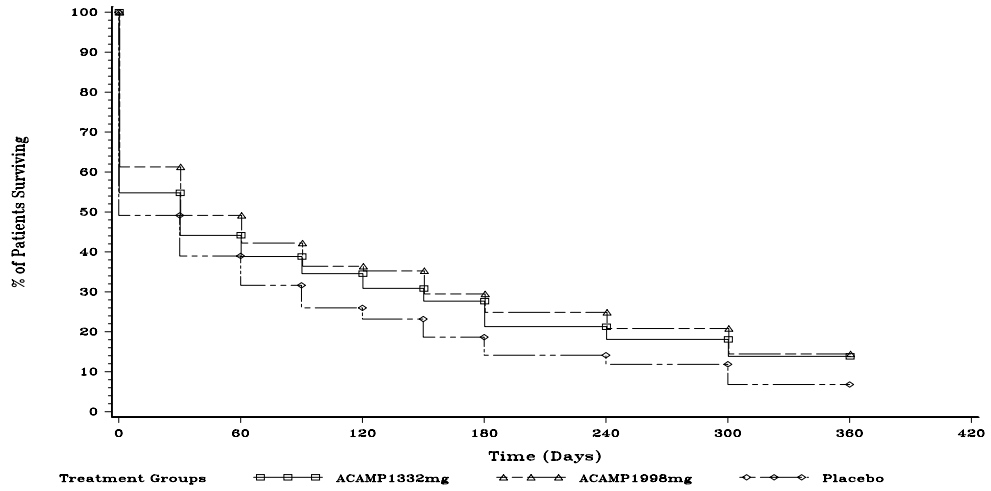


Table 5. Estimated median time and its 95%CI (days) - distribution of time to 1st relapse (Paille)§

Method	Placebo N=177	Acamp1332 mg/d N=188	Acamp1998 mg/d N=173	Log-rank (global test)
I	32 (28, 59)	35 (29, 69)	63 (55, 101)	0.0695
II	30 (0, 54)	33 (29, 63)	59 (38, 74)	0.0148
III	30 (0, 54)	33 (29, 63)	59 (38, 74)	0.0303

§ Based on the electronic data on time to first drink truncated for the treatment period.

Note that the significant difference obtained from Method III yielded a significant difference between median Acamprosate dose (1998 mg/day) vs. placebo.

CUMULATIVE ABSTINENCE DURATION (CAD)

The cumulative abstinence duration (CAD) measured the total time the patient was abstinent by the sum of all periods of complete abstinence. It takes into account all the non-relapsed days. The sponsor reported a statistically significant difference in CAD among the three treatment groups, nominal p=0.002. According to the sponsor, **if a patient did not attend for a particular visit then the patient was assumed to be non-abstinent between the visit before the missing data until the visit after.** The sponsor concluded that the statistical significance was primarily seen in the comparison between high dose Acamprosate vs. placebo (p=0.0005), and only borderline significance with low dose Acamprosate (p=0.055), this report can be found in Table 9 of the sponsor volume 1.083. This reviewer confirmed the analysis results. The estimated median days of CAD were ~5.0 months with placebo, ~6.4 months with low dose, and ~8.6 months with median dose Acamprosate, as shown in Table 6 below.

Table 6. Distribution of cumulative abstinence duration (CAD) - Paille[§]

	Placebo	Acamp1332 mg/d	Acamp1998 mg/d	p-value
Mean (SD) days	173.4 (126.1)	198.4 (133.1)	223.4 (134)	0.002
Mean (in months)	~5.8 months	~6.6 months	~7.4 months	
Median (in months)[¦]	~5.0 months	~6.4 months	~8.6 months	

[§] Extracted from Table 9 of the sponsor vol.1.083
[¦] Provided by this reviewer (note that the distribution of CAD) was not normally distributed)

PERCENTAGE OF SUCCESS

The sponsor also performed an analysis of success with three categories defined: success (defined as abstinence at day 180 and day 360), partial success (abstinence at either day 180 or day 360), and failure (not abstinent on both visits). The success rates (17% with placebo, 26% with low dose, 30% with median dose) were shown to be statistically significantly different (nominal p=0.01, can be found in Table 11 of the sponsor volume 1.083 and was confirmed by this reviewer) among the three treatment groups. It is noted that one cannot conclude whether a patient would be completely abstinent if he/she was classified as success in this analysis.

OBSERVATION PHASE **(Treatment Period + Follow-up Period)**

INCIDENCE OF COMPLETE ABSTINENCE THROUGH OBSERVATION PHASE (1.5 years)

To address the second objective "to evaluate the evolution of the therapeutic result during a 6-month period under placebo after discontinuation of randomized treatment and before ending the blind phase of the trial", this reviewer performed an analysis of complete abstinence through an additional half year observation phase. As shown in Table 7, there were no statistically significant differences observed among the three treatment groups in terms of the incidence of complete abstinence through the observation phase from treatment initiation, using all three censoring methods applied when analyzing the incidence rate during the treatment phase. Note that for Method II, a patient was considered complete abstinent if he/she had study duration at least 360 days and continuous abstinence from day 0 is at least 540 days.

Table 7. Complete abstinence rates over the observation phase - Paille

Method	Placebo (n=177)	Acamp1332mg/d (n=188)	Acamp1998mg/d (n=173)	p-value (χ2 test)
I	35 (20%)	40 (21%)	46 (27%)	0.276
II	9 (5%)	18 (10%)	19 (11%)	0.118
III	16 (9%)	24 (13%)	27 (16%)	0.175

- **SPONSOR'S CONCLUSION**

The sponsor concluded in the summary of study that 'For all principal and secondary parameters of efficacy the differences were statistically significant. There was clear evidence of a dose-response. Acamprosate 1998 mg/day was significantly better than placebo. Acamprosate 1332 mg/day failed to reach significantly better results than placebo for most main efficacy criteria, and fell midway between the results observed with the higher dose and placebo. However, there were no statistically significant differences between Acamprosate 1332 mg/day and placebo or Acamprosate 1998 mg/day. Acamprostae 1998 mg/day is a safe and effective treatment for maintaining abstinence in patients weaned off alcohol during the period immediately preceding the treatment.'

- **REVIEWER'S SUMMARY**

In this one-year treatment study, the sponsor's main objective is to compare the Acamprosate 1332 mg/day with placebo. The dropout rates (65% in placebo, 55% in Acamprosate 1332 mg/day group and 48% in Acamprosate 1998 mg/day group) and the exposure times (ranging from 8 months with placebo to 11.8 months with 1998 mg/day Acamprosate) appeared to be differential among the three groups. Under such circumstances, the CONSERVATIVE TYPE ANALYSIS (by imputing all or most of the dropouts as failure when the endpoint of interest is success) is likely to be biased in favor of the less dropped out group(s), viz.-a-viz. Acamprosate groups. Such an imputation might have given a penalty more than it should to the group with a higher dropout rate. In contrast, Method I assigning patients who discontinued early without relapse to complete abstinence might have given a favor more than it should to the group with a higher dropout rate. The truth probably lies in between. Regardless of which imputation method is applied, it can not be concluded with great confidence that the comparison between Acamprosate 1332 mg/day and placebo in complete abstinence rate was statistically significant.

The complete abstinence rate was consistently lower in placebo using all three methods. However, depending on how the abstinence status of the dropped out patients were imputed, the differences in abstinence rates were shown to be not statistically significant (p=0.285) using Method I, in which complete abstinence rates were 23%:27%:30% of placebo, low dose to median dose, respectively. Such differences became statistically significant (p=0.044) when the most conservative imputation was applied (Method II) with rates being 7%:14%:14%. These differences did not reach statistical significance when a benign imputation method was used, which only penalized dropped out patients to 'drinking' if these patients had continuous abstinence less than 340 days from treatment initiation. These complete abstinence rates, using Method III, were 11%:18%:19% of placebo, low dose and median dose, p=0.096. The complete abstinence rates were similar between Acamprosate 1332 mg/day (27%) and placebo (23%) using Method I (nominal p=0.377). These rates differed significantly using Method II (14% vs. 7%, nominal p=0.028) and not significant using the Method III (18% vs. 11%, nominal p=0.069). Regardless of which imputation method is applied, it could not be concluded with confidence that the comparison between Acamprosate 1332 mg/day and placebo in complete abstinence rate was statistically significant. This reviewer further explored the impact of the dropouts by classifying the patients into 'completer/abstinence', 'incompleter/abstinence', or 'non-abstinence' categories. It appeared that percentages of patients who were incompleter/abstinence were similar among the three groups using all three methods. This indicated that the difference between Acamprosate and placebo is likely to be from patients who were 'completer/abstinence' or 'non-abstinence irrespective of completing or incompleting the trial'. However, the data quality for the latter case is of concern, particularly, drinking diaries was not used in the study.

For time to first drink, in contrast, consistent median time to first drink was observed using all three methods whether statistically significant or not. The median times to first relapse were about two months with Acamprosate 1998 mg/day group and about one month for Acamprosate 1332 mg/day and placebo groups. For the comparison between Acamprosate 1998 mg/day vs. placebo, the Method I did not reach statistical significance and Methods II and III reached statistical significance. There was no statistically significant difference between Acamprosate 1332 mg/day vs. placebo.

The estimated median days of CAD were ~5.0 months with placebo, ~6.4 months with low dose, and ~8.6 months with median dose acamprosate. A significantly longer CAD with Acamprosate 1998mg/day was observed, but only borderline significance was observed with Acamprosate 1332mg/day as compared to placebo.

The conservative type analyses (Methods II and III) are attractive because it might be reliably used to be sure that a patient was completely abstinent during the treatment phase. Here, if a patient did not attend for a particular visit then the patient was assumed to be non-abstinent between the visit before the missing data until the visit after. Although these methods yielded a higher complete abstinence rates with Acamprosate 1332

mg/day treatment (14% or 18%) compared to placebo (7% or 11%), the median time to first drink was essentially the same between these two groups (about 30 days) using all three methods. In contrast, the higher complete abstinence rates with Acamprosate 1998 mg/day treatment (14% or 19%) were further supported by the time to first drink analyses using all three approaches and yielded twice longer median time (about 60 days) as compared to placebo or Acamprosate 1332 mg/day treatment.

The sponsor's conclusion that "Acamprosate 1332 mg/day failed to reach significantly better results than placebo for most main efficacy criteria" was consistent with this reviewer's conclusion. It is noted that the second objective of a superior complete abstinence rate with Acamprosate 1332 mg/day was not shown through the observation phase.

PRAMA

Double-blind controlled study versus placebo to assess the effectiveness and tolerance of AOTA-CA in treatment which helps to maintain abstinence after detoxification in the alcoholic patient

- **PROTOCOL SYNOPSIS**

This was a multicenter (12 psychiatric clinics in Germany under Prof. H. Sass' supervision), double-blind, randomized, placebo controlled study. Eligible patients aged 18 to 65 years with a history of at least two years (females) or three years (males) alcohol dependence, who had undergone a successful detoxification process of no withdrawal symptoms and abstinence for at least 14 days, were randomized to receive placebo or Acamprosate (AOTA-CA) for 48 weeks. Study medication was dosed stratifying on weight ≥ 60 kg vs. < 60 kg. That is, patients took 2 tablets t.i.d. containing a total of 1998 mg/day medication if heavier and 4 tablets daily containing a total of 1332 mg/day medication if lighter. Note that the distribution of baseline weights between Acamprosate and placebo was comparable. The time schedule of the study during the 48 weeks treatment phase, which was followed by an additional 48 weeks without Acamprosate therapy, was as follows.

Visit0	1	2	3	4	5	6
Initial exam	4wk	8wk	12wk	24wk	36wk	48wk

The primary objective was to investigate whether treatment with Acamprosate increases the proportion of successfully treated, i.e., **abstinent patients during the 48-week therapy phase following at least 14 days of abstinence.** The purpose of a follow-on 48 week period without the study drug was to test whether any primary benefits of the treatment outlast the therapy period.

The primary efficacy endpoint was the time when the first relapse occurs[§]. The point in time when a relapse occurs was defined as the day on which alcohol consumption starts again and was analyzed by log-rank test in which dropout patients without further information regarding treatment course would be censored at the last available information time. Secondary endpoints included (1) frequency of relapses, (2) craving, (3) transferrin. Other variables included diagnostic confirmation of alcohol dependence, disease severity, types of alcoholic drink taken, emotionality of the patient, type and intensity of accompanying non-drug therapy, patient's psychosocial situation, laboratory parameters, etc. This review focused on the drinking related efficacy outcomes.

[§] A relapse was defined as follows:
- short-term relapse: alcohol consumption for up to 24 hours
- long-term relapse: alcohol consumption for more than 24 hours with/without the need for hospitalization
- continuous relapse: constant alcohol consumption

According to the protocol (p.155 of vol.080), the primary efficacy variable 'relapse: yes/no' would be established by the investigator, whose overall assessment takes into consideration information from the patient and relatives, the result of the Breathalyzer test, the result of two typical laboratory values, as well as the investigator's own clinical impression. When discrepancies arise, the decision 'relapse: yes/no' must be substantiated. The sponsor believed that the procedure ensured sufficient validation of the investigator's decision about the occurrence of the relapse.

For sample size estimation, a 20% increase in the rate of abstinence would be regarded as clinically relevant assuming abstinence rate without medication is 50% as recognized in the literature. It was estimated that 200 patients would be needed to detect a 20% difference in abstinence rate at 1% level of significance and 80% power. In this study, 136 patients per group were the basis for analysis.

Protocol amendment on March 1991 modified exclusion criteria and included additional patient contacts in the phase where the individual examinations have a frequency of 12 weeks.

- **OVERVIEW OF THE STUDY RESULTS AND REVIEWER'S EVALUATION AND COMMENTS**

The study was initiated on October 16, 1990 and completed on December 3, 1992 (~2 years). A total of 272 patients received study medication were randomized to receive Acamprosate (n=136) or placebo (n=136). The mean age at entry was 41 years old and 78% of the patients were males. There were no significant differences between the treatment groups with regard to age, sex, weight, height, civil, living or employment status. According to the sponsor, placebo treated patients appeared to have a higher percent of family history of alcoholism (14%) than Acamprosate treated patients (9%).

- **PATIENT ACCOUNTABILITY**

Patients accountability during the treatment phase was summarized in Table 1 (submitted when seeking for approval in Europe). A total of three deaths occurred, two of them were from Acamprosate group. Details of the reason of deaths can be found in the evaluation and comments of medical review written by Dr. Cellia Winchell.

Table 1. Patient Accountability - PRAMA[§]

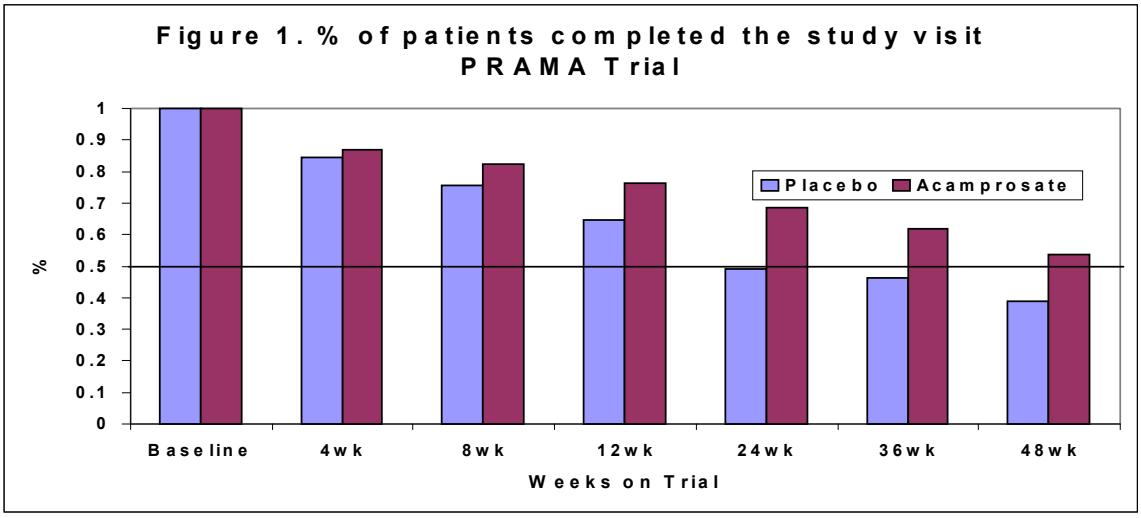
	Complete	Concomitant Illness	Death	Lost to Followup	**Patient Refusal**	Serious Aggravation	Severe AE
Placebo (n=136)	**55 (40%)**	1 (1%)	1 (1%)	28 (20%)	**45 (33%)**	5 (4%)	1 (1%)
Acamprosate (n=136)	**79 (58%)**	0 (0%)	2 (1.5%)	26 (19%)	**20 (15%)**	7 (5%)	2 (1.5%)

[§] Extracted from the sponsor's Table 2 of vol.1.079 (p.24).

The percentage of patients completed the study between placebo (40%) and Acamprosate (58%) was shown to be different, nominal p=0.0004. More patients discontinued the study early with placebo than with acamprosate. 'Patient refusal' appeared to be the major reason of discontinuation showing a difference between placebo (33%) and Acamprosate (15%), nominal p-value=0.0004. The sponsor reclassified the reasons of early discontinuation on 8 Acamprosate patients and 4 placebo patients after the European approval. Majority was reclassified to severe AE. These changes were summarized in the sponsor's final study report amendments. The amended reasons resulted in 53 (39%) completed placebo and 73 (54%) completed Acamprosate patients, nominal p=0.015. The originally observed percents of 'severe AE' had changed to 4% (5 patients) with placebo and 6% (8 patients) with Acamprosate, respectively.

The percentage of available patients over the treatment period was summarized in Figure 1.

Figure 1 % of patients completed the study visit – PRAMA Trial



- **TIME TO DISCONTINUATION**

This reviewer performed an analysis of time to discontinuation using the electronic data information on last visit date and the baseline date. Results are summarized in Table 2. The estimated median times were 169 days with placebo and 337 days with Acamprosate, nominal p=0.0054 (Wilcoxon rank sum test). On average, the Acamprosate treated patients appeared to stay on study twice longer than the placebo treated patients.

Table 2. Time to discontinuation – PRAMA Trial

	Placebo (n=136)	Acamprosate (n=136)
Last visit date – baseline date[§]		
Mean (SE)	192 days (13 days)	245 days (13 days)
Median (range)	169 days (1, 442)	337 days (1, 435)

[§] from electronic data base

- **EFFICACY IN HELPING TO MAINTAIN ABSTINENCE (treatment period)**

To evaluate total abstinence from alcohol, the sponsor reported the following four efficacy endpoints: time to first relapse, continuous abstinence rate, cumulative duration of abstinence (CAD) and the investigators global assessment of drinking behavior at each visit. The reviewer's evaluation and comments in reference to the sponsor's summary of report follow.

TIME TO FIRST RELAPSE

This was the protocol specified primary efficacy endpoint. This reviewer confirmed the sponsor's report on time to first relapse analysis using censored approach and the uncensored approach, see Table 3. The median continuous abstinence duration calculated from the uncensored approach was almost 3 times longer in the Acamprosate group (134.5 days) compared to the placebo group (45.0 days). The difference between treatment groups was statistically significant, p<0.001.

A total of 69 patients (31 in Acamprosate and 38 in placebo) discontinued the study early without having any drinking. The inclusion of these patients as censored observation in the time to first relapse analysis using the censored approach showed a similar effect on the median estimates. In both groups the median duration estimates were essentially halved using the uncensored approach as compared to the censored approach.

Results from the censored analysis showed that the median time to first drink for the Acamprosate group (253.0 days) was statistically significantly longer compared to the placebo group (92.0 days, logrank test p=0.0052), see Table 3.

Table 3. The primary efficacy endpoint: time to first relapse (PRAMA Trial)

	Placebo (n=136)	Acamprosate (n=136)	p-value
TMRELITT: RELFLAGC[1]			
Median (95% CI)	92 days (49-164)	253 days (128, NA)	0.0052 (log-rank)
censor%	40% (54/136)	51% (70/136)	0.052 (χ2)
TMRELITT: RELFLAGU[2]			
Median (95% CI)	45 days (36-75)	134.5 days (75, 157)	0.0005 (log-rank)
censor%	12% (16/136)	29% (39/136)	0.003 (χ2)

[1]: dropout without an event is considered censored (censored approach)
[2]: dropout without an event is considered relapsed (uncensored approach)

The time to first relapse analysis accounts for censoring distributions between the two treatment groups. The sponsor concluded "In the survival analysis, the mean number of days to the first relapse was 165.2 +/- 143.8 days in the Acamprosate group compared with 112.3 +/- 126.5 days in the placebo group, with 45% of patients recorded as having continuous abstinence in the Acamprosate group compared with 25% of patients in the placebo group (Log-Rank test p=0.0052)." The interpretation of the survival analysis on the time to first relapse may be problematic. The censoring distribution differed between the Acamprosate group and the placebo group. Given censoring was differential between the Acamprosate and the placebo groups, the mean time to first relapse could be misleading. In addition, 45% with Acamprosate and 25% with placebo estimated from the survival curve refers to the probability of patients who would continue to be abstinent by week-48.

COMPLETE ABSTINENCE RATE (or CONTINUOUS ABSTINENCE RATE)

Table 4. Distribution of no relapse during the treatment phase – PRAMA Trial[§]

	Method I (RELAPITT) (same as RELFLAGC) No relapse to drinking	Method II (RELFLAGU) no relapse and completed the trial	Method II (final study report amendments)
Placebo (n=136)	40% (54)	12% (16)	11% (15)
Acamprosate (n=136)	51% (70)	29% (39)	27% (37)
p-value	0.052	0.0005 (<0.001)*	0.0007

[§] Extracted from the sponsor In-text Table 8.7.2.7.3:1

This reviewer analyzed the efficacy outcome of continuous abstinence rate during the treatment phase. Results are summarized in Table 4. Similar to time to first relapse analysis, both the censored approach (Method I) and uncensored approach (Method II) were analyzed. For the Method I, percentage of patients without relapse to drinking irrespective of their completing the trial was borderline significantly higher with Acamprosate (51%) than with placebo (40%), p=0.052. The sponsor reported results using the Method II, the most conservative analysis. That is, when incompleted patients without relapsed to drinking was considered as relapsed, such percentages were 29% with Acamprosate and 12% with placebo, p=0.0005. This reviewer also performed a robustness analysis of Method II using the reclassified completer status reported in the sponsor's final study report amendment. Consistent statistical evidence was observed, p=0.0007.

To understand further the distribution of patients in terms of their status of completing the trial and relapse to drinking, this reviewer performed an analysis in which patients were classified into the following four categories: (1) completer and no relapse, (2) completer and relapse, (3) incompleter and no relapse, and (4) incompleter and relapse. Table 5 summarized the results using the Method I. The abstinence rate was twice higher with Acamprosate (31%) as compared to placebo (15%) in patients who completed the trial, and no apparent difference in patients who did not complete the trial (21% with Acamprosate and 25% with placebo).

In contrast, the lower relapse rate with Acamprosate was primarily observed in the incompleter subgroup (21% with Acamprosate and 35% with placebo) and not in the completer subgroup (27% with Acamprosate and 26% with placebo).

It is noted that placebo patient (pid=273) was classified as relapsed completer. This patient should be a relapsed incompleter. One Acamprosate patient (pid=280) was classified as not relapsed completer. This patient should be a not relapsed incompleter. Including/excluding these two patients in the appropriate categories, the results in terms of nominal statistical significance remained. The following table provides a clean picture with imputation on the dropout patients.

Table 5. Summary of patients based on their status completing the trial and their status 'abstinence' during the entire 48 weeks treatment period

Method I (RELFLAGC)	**Completer and No relapse**	Completer and Relapse	Incompleter and no relapse	**Incompleter and relapse**
Placebo (n=136)	**20 (15%)**	35 (26%)	34 (25%)	**47 (35%)**
Acamprosate (n=136)	**42 (31%)**	37 (27%)	28 (21%)	**29 (21%)**

When the Method II was applied, not relapsed incompleters were combined into the relapsed incompleters. Significantly higher abstinence rate in Acamprosate (29%) than in placebo (12%) was observed, i.e., the results shown in the column with a label heading "Method II" of Table 4 above. This reviewer further investigated the dropout reasons among the relapsed dropouts and the no relapsed dropouts. It appeared that among those dropouts who did not relapse, there was little difference in the reason of discontinuation. However, of the dropouts with relapse, the distribution of the reasons of discontinuation appeared to differ between two treatment groups, noticeably, in patients refusal (7% with Acamprosate and 24% with placebo). It appeared that differential (or informative) dropouts were observed between the relapsed placebo patients vs. relapsed Acamprosate patients.

CUMULATIVE DURATION OF ABSTINENCE

Table 6. Cumulative abstinence duration in days

CAD	Placebo (n=136)	Acamprosate (n=136)	p-value
Mean (SD) in days Median (range) in days	162.03 (132.19) 135 (6, 364)	224.62 (136.61) 270 (15, 360)	0.0002*
CADITT ≥ 360 days	13% (17)	29% (39)	0.001

* Wilcoxon 2-sample test, extracted from sponsor Table 6, p.28 of vol.1.079.

Cumulative duration of abstinence during the treatment phase was a secondary efficacy endpoint. It measured the total time the patient was abstinent by the sum of all periods of complete abstinence. The sponsor reported a significantly longer average CAD with Acamprosate (224.62 days) than with placebo (162.03 days), p=0.0002. This reviewer confirmed the results, see Table 6. This reviewer also reported the median cumulative abstinence duration days since the distribution appeared to be not normally distributed. These medians of the CAD were 135 days with placebo and 270 days with acamprosate.

Given that the placebo treated patients had less exposure to the treatment, it is likely that had the 60% placebo treated patients compared to the 42% Acamprosate treated patients continued the treatment longer, the already lower abstinence rate in placebo (40% vs. 51% with Method I, 12% vs. 29% with Method II, and 11% vs. 27% with Method III) would probably continue to be lower if not much lower.

To assess CAD as a fraction of the duration of treatment, the sponsor calculated the corrected cumulative abstinence duration (CCAD). The CCAD analysis reported by the sponsor was consistent with the CAD analysis.

- **REVIEWER'S SUMMARY**

The sponsor concluded in the study report "Acamprosate tablets, administered over 48 weeks were consistently more efficacious than placebo in maintaining abstinence in alcoholic patients previously weaned from alcohol." This reviewer confirmed the findings. The early discontinuation rates were marginally different (60% vs. 48%), whereas the corresponding times to discontinuation difference were 169 days (~5.6 weeks) with placebo and 337 days (~11.2 weeks) with acamprosate, which was nominally statistically significantly with p=0.006.

In summary, Acamprosate was shown to have longer time to first relapse, higher percentage of continuous abstinence during the treatment phase and higher percentage of cumulative abstinence rate as compared to placebo. Further investigation suggested that a higher percentage of patients completed the study without relapsed to drinking with Acamprosate (31%) compared to placebo (15%), and that among those who discontinued the study early, a lower percentage of Acamprosate treated patients (21%) relapsed compared to placebo treated patients (35%).

US96.1

Acamprosate in patients with alcohol dependence: a double-blind, placebo controlled safety and efficacy study at two active dose levels

- **STUDY SYNPOSIS**

This was a multicenter (21 US centers), double-blind, randomized, placebo controlled 3-arm 24-week study. The study was initiated in May 1997 and completed in January 1999 (~1.7 years). Eligible ambulatory patients aged 18 or older, who were alcohol dependent according to the DSM-IV criteria of the American Psychiatric Association and who had been withdrawn from alcohol or who had completed medicated detoxification within ≥2 to ≤10 days of study entry, were passively stratified on the basis of medicated (inpatient or outpatient) detoxification vs. non-medicated withdrawal and then randomized to receive placebo or Acamprosate 2000 mg/day (median dose) or Acamprosate 3000 mg/day (high dose) for 24 weeks. Subsequent to the 24 weeks treatment phase (but with continued study blinding), all subjects were to be followed for an additional two months (follow-up phase).

During the treatment phase, all patients were given standardized medication management/supportive psychotherapy at each visit by a qualified therapist and according to a protocol-specific manual, entitled "Brief Intervention and Medication Compliance Procedures". The alcohol measurement collection according to the Alcohol Timeline Follow Back (TLFB) schedule during the 24 weeks treatment phase (bolded) followed by an additional 2 months without Acamprosate therapy was as follows.

Visit0	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	V9	V10
Baseline	**Wk1**	**Wk2**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk20**	**Wk24**	Wk25	Wk32
Baseline	**Treatment (6-months)**								Follow-up (2mon)	

It is noted that after the first month of treatment, patients were contacted by telephone at weekly intervals to reinforce compliance and for supportive purposes in between their monthly regular visits. The study schema can be found in page 15 of the original protocol (p.18 of vol.1.102; also p.47 of vol.1.099).

The protocol has a section on summarizing drinking measures and related assessments. Specifically, if inconsistencies remain unresolved on alcohol consumption between sources, the most negative outcome was to be assumed. Alcohol consumption was recorded in standardized drinks. In addition, a number of efficacy assessments were usually self-reports, but for the purposes of this study, unless so-specified, the majority of the questionnaires were administered to the patient by study personnel.

The objectives were (1) to confirm efficacy and safety of oral Acamprosate tablets in US alcohol-dependent patients, at a total daily dose of 2000 mg/day (1000 mg bid) in association with standardized but minimal psychosocial support, guided by a protocol-specific manual; (2) to explore the efficacy and safety of Acamprosate at a total daily dose of 3000 mg/day (1500 mg bid); (3) to explore the efficacy and safety of Acamprosate therapy when initiated within ≥2 to ≤10 days of any hazardous drinking (>2 drinks/day for females, >3 drinks per day for males) or completion of medicated detoxification.

The primary efficacy endpoints were (1) time to first day of any drinking[1]; (2) time to first day of heavy drinking[2] (≥6 drinks for men, ≥4 drinks for women); (3) cumulative abstinence duration[3]; and (4) rate of complete abstinence[4]. Secondary efficacy endpoints were alcohol consumption, alcohol craving, gamma-glutamyl transpeptidase (GGT), clinical global impression and study retention. The primary safety endpoints were (1) review and evaluation of all treatment emergent signs and symptoms, (2) evaluation of effects on laboratory parameters, to include hematology, blood chemistries, and routine urinalysis, and (3) evaluation of any medical changes.

For sample size estimation, the sponsor indicated in the protocol that 'sample size is based on an evaluation of CAD and abstinence rates from European trials of Acamprosate. This sample size is projected to have 80% power to show a significant difference of approximately 23 days in CAD between Acamprosate 2000 mg/day and placebo." The only parameter specified in the sample size estimation was the difference in CAD of 23 days. The sponsor planned 198 patients per group in Acamprosate 2000 mg/day arm and placebo arm and 64 patients in Acamprosate 3000 mg/day exploratory dose arm. In the sponsor's NDA report, it was stated that "the study was originally projected to have 80% power to show a significant difference of 23 abstinent days (80 days versus 103 days, SD=78) between Acamprosate 2000 mg/day and placebo, assuming a 10% dropout rate." However, the dropout rates were 45% (placebo) and 59% (Acamprosate 2000 mg/day) after the trial completion.

Handling of missing data: lost-to-follow-up patients were considered "treatment failures." "Unavailable data for patients who terminate the study early for reasons other than lost to follow-up or treatment failure (e.g., patient's decision, sponsor's decision) will remain missing in all analyses."

After the final protocol (dated February 22, 1997), there were two amendments: amendment #1 related to the exclusion criteria modification and amendment #2 related to modification of the inclusion criteria.

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[1] First day of any drinking was defined as the earliest drinking episode identified by the patient or collateral informant, or by a positive breath alcohol concentration (>0.003%)

[2] First day of heavy drinking was defined as the earliest heavy drinking day (≥4 drinks for women, ≥6 drinks for men) identified by the patient or collateral informant, or by a breath alcohol concentration consistent with intoxication (>0.04%)

[3] CAD: the minimum number of abstinent (alcohol-free) days between visits, reported by the patient, collateral informant, or breath alcohol concentration results

[4] for rate of complete abstinence: non-abstinence was assumed if either the patient, collateral informant, or breath alcohol concentration indicate any alcohol consumption (≥0.003%)

- **OVERVIEW OF THE STUDY RESULTS AND REVIEWER'S EVALUATION AND COMMENTS**

The NDA report was dated November 19, 2001. Of those 741 patients screened, 601 patients were randomized to receive Acamprosate 2000 mg/day (n=258) (median dose), Acamprosate 3000 mg/day (n=83) (high dose) or placebo (n=260). The intent-to-treat population or the all efficacy population was based on 592 patients. The main interest was the comparison between Acamprosate 2000 mg/day vs. placebo and Acamprosate 3000 mg/day group was a dosage exploratory arm. The mean age at entry was 44 years and 68% of the patients were males. Baseline characteristics were comparable between the treatment groups.

- **PATIENT ACCOUNTABILITY**

Patient accountability during the treatment phase was summarized in Table 1. No death occurred in any of the three treatment arms.

Acamprosate 2000 mg/day group (41%=106/258) had the lowest percentage of patients who completed the study followed by Acamprosate 3000 mg/day (52%=43/83) and placebo (55%=143/260), nominal global p=0.0054. Numerically more patients discontinued the study early with Acamprosate than with placebo. 'Patient decision' and 'lost to follow-up' appeared to be the major reasons of discontinuation that showed an imbalance between placebo and Acamprosate 3000 mg/day group vs. Acamprosate 2000 mg/day group. Distribution of percent of patients available over the treatment period can be found in **Figure 1**.

Table 1. Patient Accountability of early discontinued patients during treatment phase – US 96.1 Trial[§]

	AE	IMP	AEC	PV	TF	**PD**	IV	SP	LFU	Othr
Placebo n=260	6 2%	1 <1%	2 <1%	1 <1%	13 5%	**54 21%**	3 1%	2 <1%	**33 13%**	2 <1%
A2000mg N=258	6 2%	4 2%	4 2%	0 0%	13 5%	**71 28%**	4 2%	1 <1%	**47 18%**	2 <1%
A3000mg N=84	2 2%	1 1%	0 0%	0 0%	4 5%	**18 22%**	4 5%	0 0%	**10 12%**	1 1%

[§] Extracted from sponsor in-text Table 6.1 of vol.1.099 (p.77); confirmed by this reviewer.
AE: adverse event; IMP: intercurrent medical/psychological event; AEC: appearance of exclusion criteria; PV: Protocol violation; TF: treatment failure; **PD: patient decision**; IV: investigator decision; SP: sponsor decision; **LFU: lost to follow-up**; Othr: other.

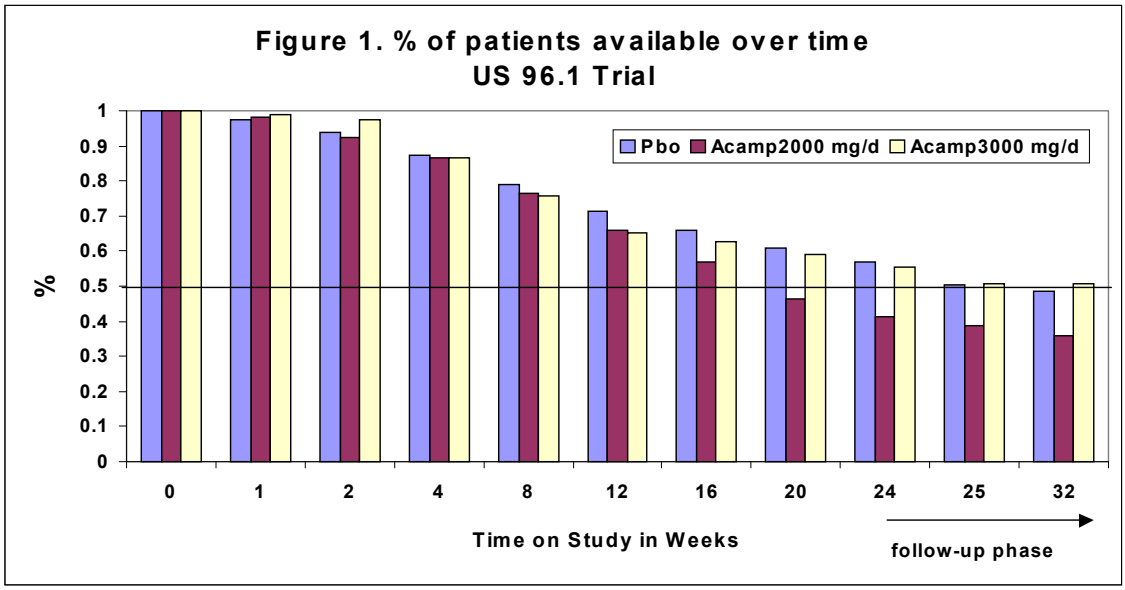


Figure 1. % of patients available over time – US 96.1 Trial

- **TIME TO DISCONTINUATION**

This reviewer performed an analysis of time to discontinuation using the electronic data information on days on study. Results are summarized in Table 2. The estimated median times were 168 days (5.6 months) with placebo and 136 days (4.5 months) with Acamprosate 2000 mg/day. Acamprosate 3000 mg/day had similar treatment exposure time (164 days) as that of placebo. A longer and similar time to discontinuations were observed for high dose Acamprosate (220 days) and placebo (211 days), but the median dose Acamprosate had the median time to discontinuation (136 days).

Table 2. Time to discontinuation in days – US96.1 Trial[§]

	Placebo N=260	Acamp 2000 mg/d N=258	Acamp 3000 mg/d N=83
Treatment phase only Median (95% CI)	168 (1, 271) days	136 (1, 249) days	164 (1, 218) days
Treatment + Follow-up phase Median (range)	211 (1, 316) days	136 (1, 299) days	220 (1, 294) days

[§] based on the electornic data information on days on study

In summary, the placebo arm and Acamprosate 3000 mg/day arm had one month longer exposure to the treatment than Acamprosate 2000 mg/day arm during the treatment phase and a total of two months longer exposure including the follow-up phase. In addition, the dropout rates were significantly higher with Acamprosate 2000 mg/day arm (59%) than with placebo (45%), nominal p=0.0015. It appeared that data indicated an informative censoring and differential dropout pattern.

- **PRIMARY EFFICACY ENDPOINTS**

The sponsor summarized the results of the protocol specified primary efficacy endpoints, see the sponsor's In-Text Table 8.7.4.1:1. This reviewer confirmed the sponsor's analysis results in the In-Text Table 8.7.4.1:1 with two minor differences. The median time to first heavy drinking was 15 days. The mean was 45.8% and the median was 39% for CCAD with Acamprosate 2000 mg/day treatment. These analysis results were based on the intent-to-treat population. The resulting p-values for the comparison between placebo and Acamprosate 2000 mg/day were 0.253 ($\chi 2$ test) for percentage of patients who relapsed to drinking (or who were completely abstinent during the treatment period), 0.596 (log-rank test) for time to first drink, 0.238 (log-rank test) for time to first heavy drink, 0.071 (Wilcoxon rank sum test) for CAD analysis, and 0.134 (Wilcoxon rank sum test) for CCAD analysis, respectively.

The median dose Acamprosate (2000 mg/day) failed to show a superior treatment effect on all the protocol specified efficacy endpoints.

According to the sponsor's report, "for the ITT Population, the proportion of patients who had undergone alcohol detoxification prior to randomization and the overall proportion of patients who were abstinent prior to starting study medication was low. The percentage of patients who had detoxification prior to randomization was 12% in the Acamprosate 1998/2000 mg/day group, 7% in the Acamprosate 3000 mg/day group, and 10% in the placebo group. In contrast to the European studies, only about 50% of the patients in all 3 groups were abstinent at Baseline." The percents of patients having a treatment goal of total abstinence were 40%, 32%, and 45% in the Acamprosate 1998/2000, Acamprosate 3000 and placebo groups.

In-Text Table 8.7.4.1:1 Summary of Originally Planned Efficacy Analyses – ITT Population – US Short-Term Supportive Efficacy Study

Parameter	Statistic	ACAMP 2000 mg/day	ACAMP 3000 mg/day	Placebo
Number of Patients Randomized	N	255	82	258
Number of Patients Who Relapsed to Drinking	n (%)	233 (92%)	74 (90%)	227 (89%)
Time to First Drink (days)	Median	4	4	4
Time to Heavy Drinking (days)	Median	14	17	12
Cumulative Abstinence Duration (CAD) (days)	N Mean (SE) Median	253 72.3 (3.7) 56	82 81.5 (7.1) 75	256 83.3 (3.9) 78
CCAD (%)	N Mean (SE) Median	253 45.5 (2.2) 38	82 49.9 (4.1) 47	256 51.2 (2.2) 53
Data Source: Final Study Report, Appendix I.10.8, Tables 5.1.1, 5.2.1, 5.3.1, 5.4.1.				

Note: Percentages are based on the number of patients randomized.

- **CHANGE OF PRIMARY EFFICACY ENDPOINT**

The sponsor argued the need to restructure the intended statistical analysis plan because European outcome parameters that were contingent on a population abstinent at baseline (e.g., time to first drink and rate of complete abstinence) were not relevant in the largely non-abstinent US sample. In the US population, patients neither achieved total abstinence at the time of randomization, nor were the expectations regarding detoxification fulfilled. In other words, 50% of the patients had not discontinued drinking at randomization (100% in European trials) and only 10% of patients underwent medicated detoxification (primarily outpatient) (100% in European trials). Details of the differences between the three European pivotal trials (Paille, Pelc II and PRAMA) and the US 96.1 Trial can be found in the Appendix – US96.1 of this review.

- **NEW PRIMARY EFFICACY ENDPOINT**

The sponsor's post-hoc defined new primary efficacy endpoint was cumulative abstinence duration[5] (CAD). The actual endpoint used for the analysis was CCAD, the corrected cumulative abstinence duration. New secondary efficacy endpoints were categorization of CAD (good, partial and poor responders), rate of complete abstinence during the last treatment phase visit interval, the change from baseline in number of standard drinks per week and number of drinking days per week, and average alcohol consumption during the treatment phase relative to baseline. **Note that for all efficacy parameters, information on daily drinking was based primarily on the patient's Alcohol Timeline Follow Back Interview.**

The sponsor defined five populations of interest. They are (1) **ITT population** (all randomized patients who took at least one dose of double-blind study medication), (2) **safety population** (all patients in the safety

[5] Treatment phase CAD was defined as the percentage of abstinent days while on study drug. For patients whose discontinuation was determined to be associated with alcohol use, the denominator for the Treatment Phase CAD was the anticipated duration of the Treatment Phase (the "uncensored" duration). The anticipated duration was calculated as the actual time on treatment plus the anticipated time required to complete all remaining visits per the protocol schedule. For patients whose discontinuation was determined to not be associated with alcohol use, the denominator of the treatment phase CAD was the actual time the patient participated in the study (the "censored" duration).

population but for whom some post-baseline efficacy data were recorded), (3) **efficacy evaluable population** (EFF, all randomized patients who took double-blind study medication for at least 7 days, returned for at least one post-baseline visit, did not have a positive urine test for a drug of abuse at any time after randomization, and were at least 75% compliant for the duration of their participation in the treatment phase, (4) **motivated ITT population** (all patients in the ITT population who had a treatment goal of complete abstinence), (5) **motivated EFF population** (all patients in the EFF population who had a treatment goal of complete abstinence).

CCAD (Corrected Cumulative Abstinence Duration)

According to the sponsor, "For the purposes of statistical testing of CCAD, models were fit via ANCOVA [Neter J, Wasserman W, Kutner M. Applied linear statistical models. Richard D. Irwin, Inc, Homewood, Illinois, 1990:861-906] to ranked data because of the nonnormal distribution of CCAD. All reported p-values are from analyses of the ranked response values. CCAD was statistically significantly greater ($p \leq 0.044$) in the Acamprosate 1998/2000 mg/day group compared to the placebo groups in all 4 analysis populations after adjusting for baseline covariates (pooled site, baseline CGI-severity, stage of readiness to change, psychological antecedent, addiction index, and goal of abstinence) and treatment exposure (defined as study drug compliance multiplied by treatment duration divided by 100). In a second model excluding treatment exposure, the difference between the Acamprosate 1998/2000 mg/day and placebo groups approached statistical significance for the Motivated ITT and Motivated EFF populations ($p=0.100$ and $p=0.068$, respectively). Differences between the Acamprosate 1998/2000 mg/day and placebo groups for the least-squares means from both models were greater for the Motivated ITT and Motivated EFF populations compared to the ITT and EFF populations."

In-Text Table 8.7.4.7:2 Corrected Cumulative Abstinence Duration (CCAD) (%): Treatment Group Comparisons and Adjusted Means – US Short-Term Supportive Efficacy Study – All Efficacy Popns

Population	Statistic	ACAMP 1998/2000 mg/day	Placebo	P-Value
Intent-to-Treat	n	253	256	
	LSMean (1)	58.2	52.3	0.044*
	LSMean (2)	56.8	53.4	0.296
Efficacy Evaluable	n	177	198	
	LSMean (1)	62.3	54.8	0.023*
	LSMean (2)	60.6	55.8	0.157
Motivated Intent-to-Treat	n	100	115	
	LSMean (1)	70.0	58.1	0.021*
	LSMean (2)	68.3	59.0	0.100
Motivated Efficacy Evaluable	n	71	86	
	LSMean (1)	75.5	59.4	0.008**
	LSMean (2)	73.0	61.3	0.068
Data Source: Table 8.7.3.5.1, US study report Tables 5.1.1 and 5.1.3.				

* Significant at the 0.050 level; ** significant at the 0.010 level. The test was based on the ranked ANCOVA.
Note: LSMean (1) was obtained from an ANCOVA model including treatment exposure, pooled site, Baseline CGI-severity, stage of readiness to change, psychological antecedent, addiction index, and goal of abstinence.
LSMean (2) was obtained from the same model with the exclusion of treatment exposure. P-values from both models were based on a rank ANCOVA with the specified effects.

- **REVIEWER'S EVALUATION AND COMMENTS**

The post-hoc ANCOVA model#1 chosen by the sponsor included seven covariates. In a subsequent submission dated March 20, 2002, the sponsor provided a detailed explanation of the covariates. They were
(1) treatment exposure – compliance x treatment duration / 100
(2) pooled site (identified in the analysis plan), 3 sites which randomized <15 patients were pooled into one
(3) baseline CGI-severity – CGI severity at baseline ranges from 1 to 7
(4) stage of readiness to change – composed of 3 scales: precontemplation, contemplation and action
(5) psychological antecedent – dependent on 3 questions from the Psychiatric History in CRF, 1: at least one of the antecedents had occurred, 0: otherwise
(6) addiction index – FTND5CAT x IDUICAT. FTND5CAT was based on the baseline total for the Fagerstrom Test for Nicotine Dependence, for which possible values range from 0 to 10 and was recoded to 0 to 4. IDUICAT, based on the Illicit Drug Use Index (ranged from 0 to >1000) was recoded to 0 to 3
(7) goal of abstinence – 1: if a patient's treatment goal was complete abstinence, 0: otherwise

The post-hoc ANCOVA model#2 chosen by the sponsor contained six covariates, which excluded treatment exposure from model#1 stated above.

Significant contributions of the covariates in the ANCOVA Model#1 were Treatment (global p-value=0.02), RCQSTAGE (nominal p=0.01), PSYANT2L (p=0.01), ABSGOAL (p<0.0001) and treatment exposure (p<0.0001). In contrast, in addition to those significant covariates observed in Model#1, ADDICIN5 (addiction index) (p=0.003) became significant but the treatment effect (global p=0.0669) disappeared in the ANCOVA Model#2, which excluded the treatment exposure covariate that is potentially related to outcome measures.

Appropriateness of the Model #1 is of concern. First, the CCAD (or the PDA percent duration of abstinence) was calculated by adjusting the cumulative abstinence days (CAD) for the discontinuation of alcohol. Thus, treatment exposure has been accounted for in the CCAD derivation. By including in the model the treatment exposure as an independent covariate (while it should not be because it is potentially treatment related because of differential time of discontinuation and differential dropout), it is questionable whether the resulting estimated treatment difference can be unambiguously interpreted. The inclusion of the seven covariates was not pre-specified in the protocol. In addition, how the cutoff values of these derived covariates (excluding pooling centers, which were pre-specified in the protocol) were selected was not discussed in the protocol either. It is noted that the patient numbers were reasonably balanced across the centers, e.g., 3% to 4% were from Volpicelli site, and 4% to 5% were from O'Malley site, 6% to 7% from Anton site, 7% from Mason site, etc. The original Naltrexone drug approval was based on Volpicelli et al. trial and O'Malley et al. trial.

Table 3. Corrected Cumulative Abstinence Duration (CCAD) (%): Treatment Group Comparisons and Adjusted Means – US Short-Term Supportive Efficacy Study – All Efficacy Populations (ITT)

Intent-to-treat Population	**Placebo**	**Acamprosate 2000 mg/d (median dose)**	**Acamprosate 3000 mg/d (high dose)**	**p-value median: pbo**	**p-value[¦] high:pbo**
N	256	253	82		
Unadjusted mean[§]	54.3	56.1	60.7	0.703	0.205
Unadjusted median[§]	59	59	63		
LS Means #1[§]	52.3	58.2	62.7	0.044	0.009
LS Means #2[§]	53.4	56.8	63.1	0.296	0.021

[§] Extracted from the In-Text Sponsor Table 6.12 and Table 6.13 of vol.1.099 based on ranked ANCOVA, confirmed by this reviewer.
[¦] The nominal p-value under the column heading "p-value high:pbo" was provided by this reviewer

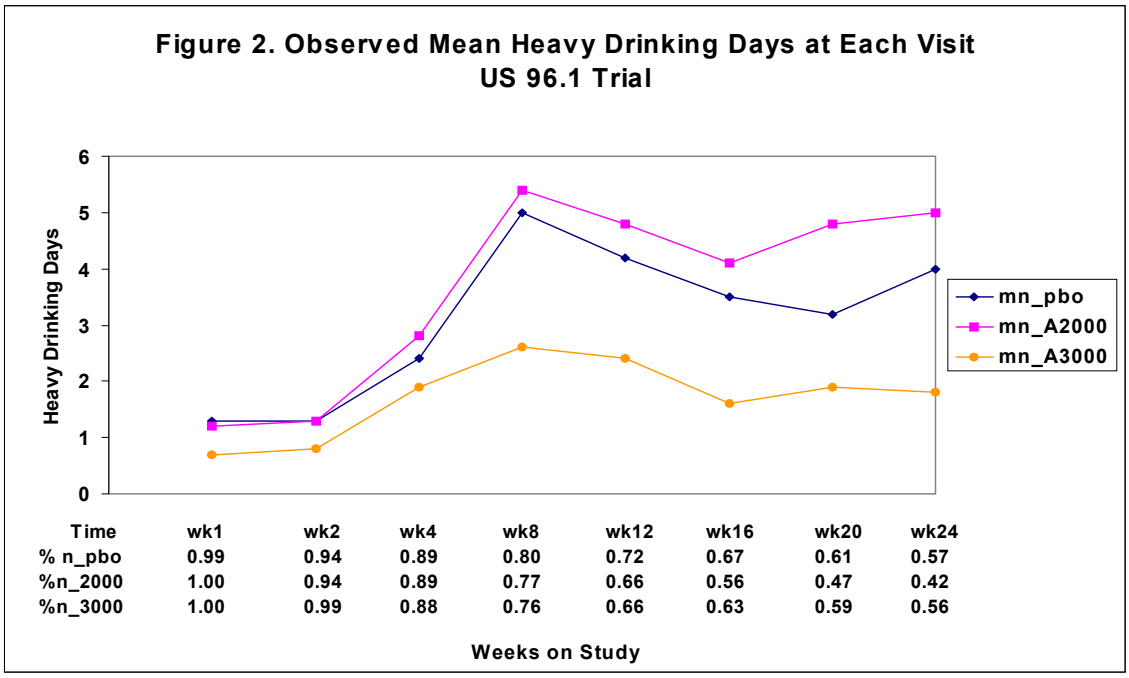
Excluding the treatment exposure, as those labeled "the Model #2", the treatment effect was no longer statistically significant (p-value is large). This reviewer further explored the ANCOVA analyses by always including the treatment effect term and the pooled center term in the model. When one covariate was included,

none of the models showed a significant Acamprosate median dose effect, even adjusted only for the potentially outcome related treatment exposure or only for the treatment goal. It was the combination of treatment goal and treatment exposure that began to appear to show a significant Acamprosate median dose effect. In fact, inclusion of a subset of the five covariates would sometimes appear to show a statistically significant median dose effect, but not always so.

The Acamprosate 2000 mg/d group and the placebo group had the same raw median value of CCAD, see Table 3. Although there was only 1/3 of the sample size for Acamprosate 3000 mg/day group as compared to the Acamprosate 2000 mg/d and the placebo, the estimated median CCAD was numerically higher. Patients treated with Acamprosate 3000 mg/day began to show a significantly higher percentage CAD after adjustment for the treatment goal. The effect became clearer after adjustment for treatment goal in addition to the stage of readiness to change, the psychological antecedent, and the addiction index individually.

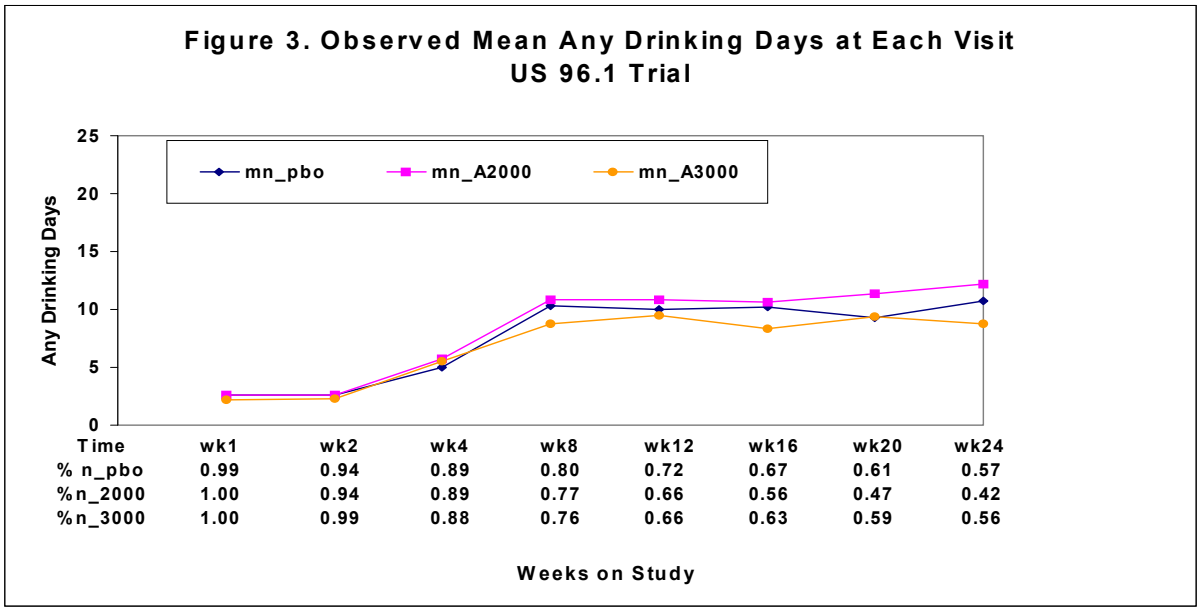
This reviewer also explored repeated measure analysis and GEE analysis on the total heavy drinking days and on the total any drinking days efficacy outcomes. There was no significant Acamprosate 2000 mg/day effect over time. An apparently significant Acamprosate 3000 mg/day effect was observed based on the heavy drinking days, but not on the any drinking days.

Figure 2. Observed mean on heavy drinking days at each study visit –US 96.1 Trial



When the data were summarized at each visit alone on the observed data, as shown in the Figure 2 (heavy drinking days), it appeared that the Acamprosate 2000 mg/day group showed a consistently larger mean heavy drinking days and a numerically similar or larger median heavy drinking days as compared to the placebo group. Although the Acamprosate 3000 mg/day group had only 1/3 of the patient size compared to the Acamprosate 2000 mg/day and placebo groups, a much lower number of heavy drinking days across all the visits appeared to be evident. In contrast, the distribution of any drinking days at each visit was comparable among all the 3 treatment groups although the Acamprosate 3000 mg/day group seemed to have numerically lower number of any drinking days, as depicted in Figure 3.

Figure 3. Observed mean on any drinking days at each study visit – US 96.1 Trial



- **SAFETY**

According to the sponsor, no deaths occurred. The overall incidence of adverse events, serious adverse events, and premature withdrawals due to adverse events was similar among treatment groups. Overall, the most frequent adverse events were **diarrhea** and **headache**, but **only diarrhea had a higher incidence in the Acamprosate treatment groups**. Diarrhea was reported by 18% in placebo, 33% in Acamprosate 2000 mg/day group and 40% in Acamprosate 3000 mg/day group, nominal $p< 0.001$. Diarrhea, as either a primary or secondary reason, resulted in premature study termination in 2% with low dose acamprosate, 2% with high dose acamprostae, and <1% with placebo. Details of the safety evaluation can be found in the medical safety reviewer's review and evaluation document.

- **REVIEWER'S SUMMARY**

There were significantly more dropouts in the primary treatment comparison arm (Acamprosate 2000 mg/day) as compared to placebo or Acamprosate 3000 mg/day exploratory treatment arm. These dropout rates were 59%, 48% and 45% for the Acamprosate median dose, high dose and placebo, respectively. In addition, treatment exposure time was one month shorter with the primary treatment group than with the high dose and placebo groups during the treatment period and two months shorter through the follow-up period. Acamprosate 2000 mg/day treatment failed to show a significant treatment effect based on the originally defined primary efficacy endpoints. The post-hoc defined CCAD adjusted for the discontinuation of alcohol and the post-hoc defined and included covariates (baseline CGI-severity, stage of readiness to change, psychological antecedent, addiction index, and goal of complete abstinence) or potentially treatment related treatment exposure were carefully assessed. It appeared that partial inclusion of the post-hoc covariates may or may not reach a statistically significant effect with Acamprosate 2000 mg/day compared to placebo. It is noted that the primary comparison of interest in this US trial was the median dose Acamprosate (2000 mg/day) versus the placebo. This study did not show an effect of Acamprosate 2000 mg/day treatment without any adjustment on the covariates. Adjustment of treatment goal alone (a subjective covariate) or treatment exposure alone (an outcome related covariate) still failed to demonstrate a significant Acamprosate 2000 mg/day effect.

From the repeated measure analysis, the GEE analysis and the cross sectional analysis of the total heavy drinking days and the total any drinking days, no statistically significant Acamprosate 2000 mg/day effect was observed. Acamprosate 2000 mg/day appeared to have numerically similar or more heavy drinking days than the placebo. The details were provided on page 32.

Although Acamprosate 3000 mg/day treatment was only an exploratory arm and had only 1/3 of the patient size, it has comparable dropout rate and treatment exposure compared to the placebo. It appeared that this high dose arm might have a favorable (often statistically significant) higher percent of cumulative abstinence duration, lower number of heavy drinking days over time and have similar number of any drinking days over time.

3 CONCLUSION

Four placebo controlled studies (Pelc II, Paille, PRAMA and US 96.1) were considered pivotal trials by FDA. All four studies appeared to show differential dropouts. In particular, all three European studies had higher dropout rates in the placebo group than the Acamprosate group(s). In contrast, the US study had significantly more dropouts and shorter treatment exposure in the primary comparison treatment arm (Acamprosate 2000 mg/day) as compared to placebo and the exploratory treatment arm (Acamprosate 3000 mg/day).

The European trials did not have the timeline follow back drinking data. The 3-month study (Pelc II) showed a significant Acamprosate (1332 mg/d and 1998 mg/d) effect on abstinence rates based on both the LOCF type and the conservative type analyses.

The 1-year (360 days) study (Paille) failed to show a significant Acamprosate effect on 1332 mg/d dose group (the primary comparison group) for most main efficacy criteria (also stated in the sponsor's conclusion), although a seeming Acamprosate effect on 1998 mg/d dose group was observed). It is noted that the second objective of showing a superior complete abstinence rate with Acamprosate (1332 mg/d and 1998 mg/d) was not achieved through the observation phase.

The 48-weeks (1-year) study (PRAMA) showed that Acamprosate had a longer time to first relapse, a higher percentage of continuous abstinence during the treatment phase and a higher percentage of cumulative abstinence rate as compared to placebo. Further investigation suggested that there appeared to be a higher percentage of patients completing the study without relapsed to drinking with Acamprosate (31%) compared to placebo (15%), and that among those who discontinued the study early there appeared to be a lower percentage of Acamprosate treated patients (21%) relapsed compared to placebo treated patients (35%). The Acamprosate arm included patients administered with 1332 mg/d dosage and 1998 mg/d dosage, depending on patients' baseline weight ($\geq$60 kgs vs. < 60 kgs), in this study.

The 24-weeks (6-months) study (US 96.1), however, had the timeline follow back drinking data. Not all patients were abstinent at baseline. About 50% of the patients had not discontinued drinking at randomization (100% in European trials) and only 10% of patients underwent medicated detoxification (primarily outpatient) (100% in European trials). It appeared that data indicated an informative censoring and differential dropout pattern. The median dose Acamprosate (2000 mg/day) (the primary comparison treatment arm) failed to show a superior treatment effect on all the protocol specified efficacy endpoints.

This study did not show an effect of Acamprosate 2000 mg/day treatment without any adjustment on the covariates. Post-Hoc adjustment of treatment goal (a subjective covariate) alone or treatment exposure (a potential treatment related variable because of differential time to discontinuation and differential dropout) alone still failed to demonstrate a significant Acamprosate 2000 mg/day effect. It appeared that partial inclusion of the post-hoc covariates may or may not reach a statistically significant effect with Acamprosate 2000 mg/day compared to placebo. The insignificant results were further supported by the repeated measure

analysis and the GEE analysis and the cross sectional analysis of the total heavy drinking days and the total any drinking days.

Although Acamprosate 3000 mg/day treatment was only an exploratory arm and had only 1/3 of the patient size, it has comparable dropout rate and treatment exposure compared to the placebo. It appeared that this high dose arm might have a favorable (often statistically significant) higher percent of cumulative abstinence duration, lower number of heavy drinking days over time and have similar number of any drinking days over time.

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This review consists of 37 pages including the Appedix

4 APPENDIX

US 96.1

Table 8.7.4.4:1 Demographic Characteristics at Baseline – US Short-Term Supportive Efficacy Study ITT Pop.

Characteristic	Statistic	ACAMP 1998/2000 mg/day (N=253)	ACAMP 3000 mg/day (N=82)	Placebo (N=257)
Gender	n	253	82	257
Males	n (%)	176 (70%)	59 (72%)	166 (65%)
Females	n (%)	77 (30%)	23 (28%)	91 (35%)
Age (years)	n	253	82	257
	Mean (SE)	44.9 (0.7)	43.6 (1.0)	44.4 (0.6)
	Min., Max.	23, 72	21, 66	22, 69
Age Distribution (years)	n	253	82	257
16-39	n (%)	82 (32%)	27 (33%)	88 (34%)
40-59	n (%)	143 (57%)	50 (61%)	139 (54%)
≥ 60	n (%)	28 (11%)	5 (6%)	30 (12%)
Weight (kg)	n	252	82	257
	Mean (SE)	80.7 (1.0)	80.9 (1.9)	78.9 (1.0)
	Min, Max	51, 134	48, 136	46, 134
Marital Status	n	253	82	257
Married	n (%)	117 (46%)	34 (41%)	133 (52%)
Not Married	n (%)	136 (54%)	48 (59%)	124 (48%)
Detoxification Prior to Randomization	n	253	82	257
Yes	n (%)	31 (12%)	6 (7%)	25 (10%)
No	n (%)	222 (88%)	76 (93%)	232 (90%)
Abstinent at Baseline	n	253	82	257
Yes	n (%)	132 (52%)	40 (49%)	127 (49%)
No	n (%)	121 (48%)	42 (51%)	130 (51%)
Duration of Alcohol Dependence/Abuse (years)	n	253	82	257
	Mean (SE)	13.0 (0.6)	12.5 (1.0)	12.6 (0.5)
	Min., Max.	1, 42	1, 40	1, 41
<10	n (%)	101 (40%)	30 (37%)	107 (42%)
≥10	n (%)	152 (60%)	52 (63%)	150 (58%)
Average Standard Drinks per day in Recent Past	n	253	82	257
<5	n (%)	62 (25%)	32 (39%)	71 (28%)
5-10	n (%)	115 (45%)	25 (30%)	111 (43%)
>10	n (%)	76 (30%)	25 (30%)	75 (29%)
Prior treatments or detoxes for Alcoholism	n	253	82	257
0	n (%)	171 (68%)	59 (72%)	192 (75%)
1	n (%)	35 (14%)	11 (13%)	27 (11%)
2	n (%)	21 (8%)	7 (9%)	8 (3%)
3	n (%)	7 (3%)	2 (2%)	16 (6%)
>3	n (%)	19 (8%)	3 (4%)	14 (5%)
Data Source: Table 8.7.3.2.1, Table 8.7.3.3.1				

Note: Percentages are based on the number of patients in the ITT population with an assessment.

DIFFERENCES BETWEEN THE US AND EUROPEAN (PAILLE, PRAMA, PELC II) STUDIES

Comparing the ITT population of the US study to the ITT population in the 3 pivotal efficacy studies with regard to these characteristics, several observations are worth noting. The percentage of males was smaller in the US (68%) study compared to the 3 pivotal efficacy studies (80% across the studies). Patients in the US study were of a similar age to patients in the 3 pivotal efficacy studies (mean age of 45 years in the US compared to 42 years in the pivotal studies). Patients in the US study were heavier (mean body weight of 80 kg) than patients in the 3 pivotal efficacy studies (mean body weight of 71 kg). Only 10% of patients in the US study had undergone detoxification prior to randomization compared to 100% of patients in the pivotal efficacy studies (by virtue of the recruitment process). The mean duration of alcohol dependence was greater in the US study (13 years) than in the pivotal efficacy studies (10 years), but patients in the US study drank much less at Baseline (30% drank more than 10 standard drinks [12 g of pure alcohol per standard drink] per day) than patients in the pivotal efficacy studies (73% drank more than 10 standard drinks per day). Fewer patients in the US study (29%) had at least 1 prior treatment or detoxification for alcoholism than in the pivotal efficacy studies (58%). Another very important difference in the Baseline characteristics in this study compared to the pivotal efficacy studies was that only 51% of patients in the US study were abstinent at Baseline, while virtually all of the patients in the pivotal efficacy studies were abstinent at Baseline. Summary of the differences are listed below.

Dosage form

- In European trials, Acamprosate was administered as a 333 mg tablet formulation given 3 times daily, primarily at a total daily dose of 1998 mg/d (two 333 mg tablets tid) or 1332 mg/d (one 333 mg tablets tid);
- In the US trial, Acamprosate was administered as a 500 mg tablet formulation given twice daily, primarily at a total daily dose of 2000 mg/day (two 500 mg tablets bid) or 3000 mg/day (three 500 mg tablets bid).

Criteria of total abstinence at study entry

- In European trials, total abstinence was explicitly required for admission to the study
- In the US trial, ambulatory outpatients with alcohol dependence who had no hazardous drinking (> 2 drinks per day for females; >3 drinks per day for males) or who had completed medicated detoxification without ≥2 to ≤10 days of randomization and who expressed a desire to cut down or stop drinking" were enrolled

Medicated detoxification

- In European trials, patients were required to undergo medicated detoxification typically inpatient
- In the US trial, not all patients were undergone medicated detoxification. The study was passively stratified prior to randomization to assure equivalent distribution of detoxified patients across treatment groups (only 10% of patients underwent medicated detoxification primarily outpatient)

Patients' baseline characteristics

- In European trials, age limit (18 to 65 years of age)
- In the US trial, there was no upper age limit, allowance for non-dependent cannabis use at enrollment and other illicit drug use during the study

Psychosocial support

- In European trials, followed a more naturalistic approach, with variable non-structured psychosocial therapy, reflective of the individual practice techniques of the participating site
- In US trial, all participating patients received standardized, manual-guided psychosocial support, consisting of brief intervention and medication compliance procedures of established efficacy to support abstinence

Other design features of the US study which were not typical of the European studies

- Daily drinking diaries, maintained by the patient and received with the therapist at each visit in conjunction with returned study medication
- Specially designed "reminder" blister packaging of study medication
- Advertising to recruit study participants from outside the existent clinical practice of participating site
- Weekly telephone contacts with study participants to supplement the monthly visit to the site
- Contracts with a close friend or relative specified by the patient to evaluate the patient's progress
- Mandatory follow-up algorithms for missed visits or missed telephone contacts, which included frequent attempts to contact the patient or collateral informant via phone and certified mail